4. The Adult Stem Cell

For many years, researchers have been seeking to understand the body's ability to repair and replace the cells and tissues of some organs, but not others. After years of work pursuing the how and why of seemingly indiscriminant cell repair mechanisms, scientists have now focused their attention on adult stem cells. It has long been known that stem cells are capable of renewing themselves and that they can generate multiple cell types. Today, there is new evidence that stem cells are present in far more tissues and organs than once thought and that these cells are capable of developing into more kinds of cells than previously imagined. Efforts are now underway to harness stem cells and to take advantage of this new found capability, with the goal of devising new and more effective treatments for a host of diseases and disabilities. What lies ahead for the use of adult stem cells is unknown, but it is certain that there are many research questions to be answered and that these answers hold great promise for the future.

What Is an Adult Stem Cell?

Adult stem cells, like all stem cells, share at least two characteristics. First, they can make identical copies of themselves for long periods of time; this ability to proliferate is referred to as long-term self-renewal. Second, they can give rise to mature cell types that have characteristic morphologies (shapes) and specialized functions. Typically, stem cells generate an intermediate cell type or types before they achieve their fully differentiated state. The intermediate cell is called a precursor or progenitor cell. Progenitor or precursor cells in fetal or adult tissues are partly differentiated cells that divide and give rise to differentiated cells. Such cells are usually regarded as "committed" to differentiating along a particular cellular development pathway, although this characteristic may not be as definitive as once thought [82] (see Figure 4.1. Distinguishing Features of Progenitor/**Precursor Cells** and Stem Cells).

EXHIBIT "A"

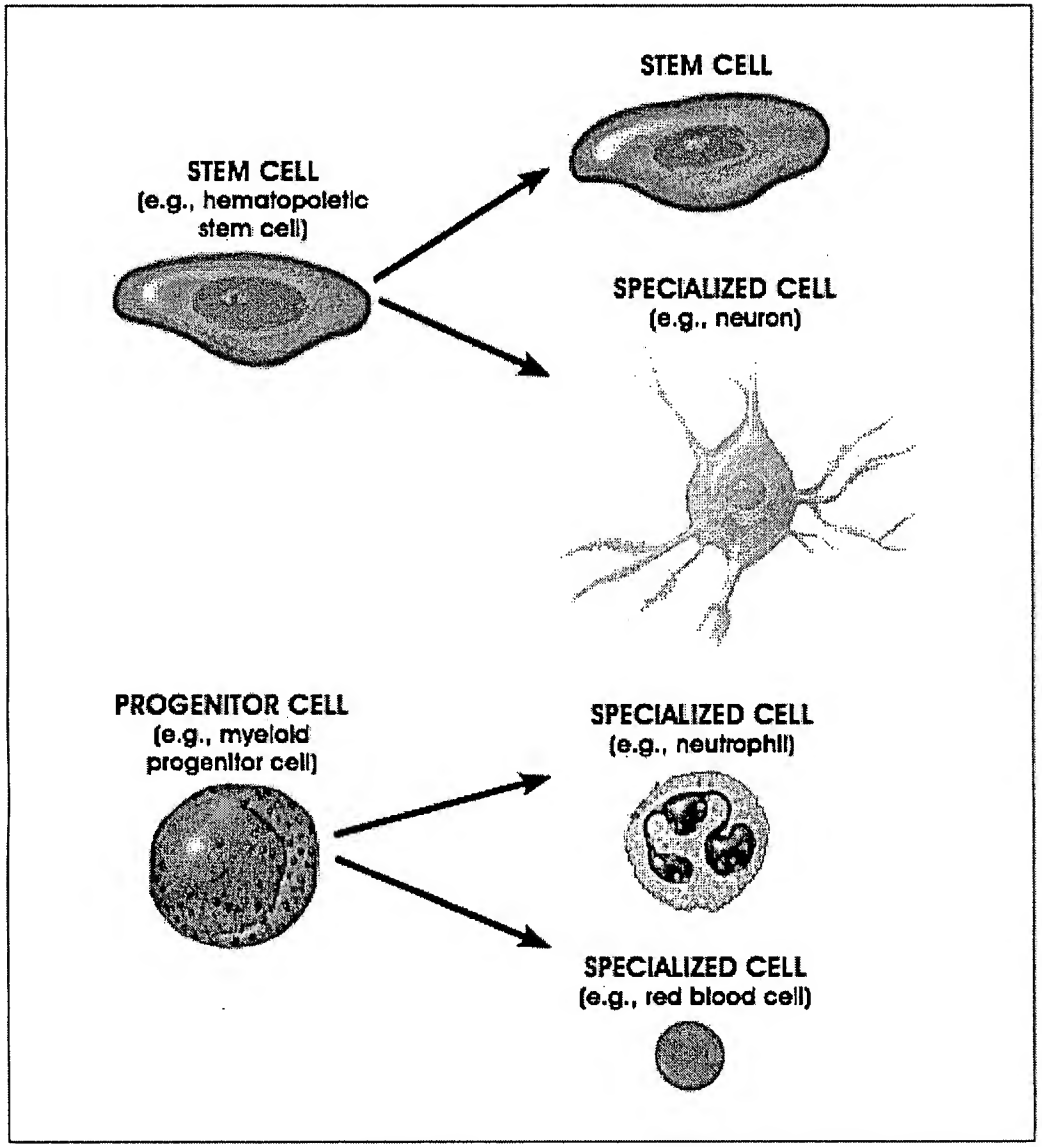

Figure 4.1. Distinguishing Features of Progenitor/Precursor Cells and Stem Cells. A stem cell is an unspecialized cell that is capable of replicating or self renewing itself and developing into specialized cells of a variety of cell types. The product of a stem cell undergoing division is at least one additional stem cell that has the same capabilities of the originating cell. Shown here is an example of a hematopoietic stem cell producing a second generation stem cell and a neuron. A progenitor cell (also known as a precursor cell) is unspecialized or has partial characteristics of a specialized cell that is capable of undergoing cell division and yielding two specialized cells. Shown here is an example of a myeloid progenitor/precursor undergoing cell division to yield two specialized cells (a neutrophil and a red blood cell).

Adult stem cells are rare. Their primary functions are to maintain the steady state functioning of a cell—called homeostasis—and, with limitations, to replace cells that die because of injury or disease [44, 58]. For example, only an estimated 1 in 10,000 to 15,000 cells in the bone marrow is a hematopoietic (bloodforming) stem cell (**HSC**) [105]. Furthermore, adult stem cells are dispersed in tissues throughout the mature animal and behave very differently, depending on their local environment. For example, HSCs are constantly being generated in the bone marrow where they differentiate into mature types of blood cells. Indeed, the primary role of HSCs is to replace blood cells [26] (see Chapter 5. Hematopoietic Stem Cells). In contrast, stem cells in the small intestine are stationary, and are physically separated from the mature cell types they generate. Gut epithelial stem cells (or precursors) occur at the bases of crypts—deep invaginations between the mature, differentiated epithelial cells that line the lumen of the intestine. These epithelial crypt cells divide fairly often, but remain part of the stationary group of cells they generate [93].

Unlike embryonic stem cells, which are defined by their origin (the inner cell mass of the blastocyst), adult stem cells share no such definitive means of characterization. In fact, no one knows the origin of adult stem cells in any mature tissue. Some have proposed that stem cells are somehow set aside during fetal development and restrained from differentiating. Definitions of adult stem cells vary in the scientific literature range from a simple description of the cells to a rigorous set of experimental criteria that must be met before characterizing a particular cell as an adult stem cell. Most of the information about adult stem cells comes from studies of mice. The list of adult tissues reported to contain stem cells is growing and includes bone marrow, peripheral blood, brain, spinal cord, dental pulp, blood vessels, skeletal muscle, epithelia of the skin and digestive system, cornea, retina, liver, and pancreas.

In order to be classified as an adult stem cell, the cell should be capable of self-renewal for the lifetime of the organism. This criterion, although fundamental to the nature of a stem cell, is difficult to prove *in vivo*. It is nearly impossible, in an organism as complex as a human, to design an experiment that will allow the fate of candidate adult stem cells to be identified *in vivo* and tracked over an individual's entire lifetime.

Ideally, adult stem cells should also be clonogenic. In other words, a single adult stem cell should be able to generate a line of genetically identical cells, which then gives rise to all the appropriate, differentiated cell types of the tissue in which it resides. Again, this property is difficult to demonstrate *in vivo*; in practice, scientists show either that a stem cell is clonogenic *in vitro*, or that a purified population of candidate stem cells can repopulate the tissue.

An adult stem cell should also be able to give rise to fully differentiated cells that have mature phenotypes, are fully integrated into the tissue, and are capable of specialized functions that are appropriate for the tissue. The term phenotype refers to all the observable characteristics of a cell (or organism); its shape (morphology); interactions with other cells and the non-cellular environment (also called the extracellular matrix); proteins that appear on the cell surface (surface **markers**); and the cell's behavior (e.g., secretion, contraction, synaptic transmission).

The majority of researchers who lay claim to having identified adult stem cells rely on two of these characteristics—appropriate cell morphology, and the demonstration that the resulting, differentiated cell types display surface markers that identify them as belonging to the tissue. Some studies demonstrate that the differentiated cells that are derived from adult stem cells are truly functional, and a few studies

show that cells are integrated into the differentiated tissue in vivo and that they interact appropriately with neighboring cells. At present, there is, however, a paucity of research, with a few notable exceptions, in which researchers were able to conduct studies of genetically identical (clonal) stem cells. In order to fully characterize the regenerating and self-renewal capabilities of the adult stem cell, and therefore to truly harness its potential, it will be important to demonstrate that a single adult stem cell can, indeed, generate a line of genetically identical cells, which then gives rise to all the appropriate, differentiated cell types of the tissue in which it resides.

Evidence for the Presence of Adult Stem Cells

Adult stem cells have been identified in many animal and human tissues. In general, three methods are used to determine whether candidate adult stem cells give rise to specialized cells. Adult stem cells can be labeled *in vivo* and then they can be tracked. Candidate adult stem cells can also be isolated and labeled and then transplanted back into the organism to determine what becomes of them. Finally, candidate adult stem cells can be isolated, grown *in vitro* and manipulated, by adding growth factors or introducing genes that help determine what differentiated cells types they will yield. For example, currently, scientists believe that stem cells in the fetal and adult brain divide and give rise to more stem cells or to several types of precursor cells, which give rise to nerve cells (neurons), of which there are many types.

It is often difficult—if not impossible—to distinguish adult, tissue-specific stem cells from progenitor cells, which are found in fetal or adult tissues and are partly differentiated cells that divide and give rise to differentiated cells. These are cells found in many organs that are generally thought to be present to replace cells and maintain the integrity of the tissue. Progenitor cells give rise to certain types of cells—such as the blood cells known as T lymphocytes, B lymphocytes, and natural killer cells—but are not thought to be capable of developing into all the cell types of a tissue and as such are not truly stem cells. The current wave of excitement over the existence of stem cells in many adult tissues is perhaps fueling claims that progenitor or precursor cells in those tissues are instead stem cells. Thus, there are reports of endothelial progenitor cells, skeletal muscle stem cells, epithelial precursors in the skin and digestive system, as well as some reports of progenitors or stem cells in the pancreas and liver. A detailed summary of some of the evidence for the existence of stem cells in various tissues and organs is presented later in the chapter.

Adult Stem Cell Plasticity

It was not until recently that anyone seriously considered the possibility that stem cells in adult tissues could generate the specialized cell types of another type of tissue from which they normally reside—either a tissue derived from the same embryonic germ layer or from a different germ layer (see Table 1.1. Embryonic Germ Layers From Which Differentiated Tissues Develop). For example, studies have shown that blood stem cells (derived from mesoderm) may be able to generate both skeletal muscle (also derived from mesoderm) and neurons (derived from ectoderm). That realization has been triggered by a flurry of papers reporting that stem cells derived from one adult tissue can change their appearance and assume characteristics that resemble those of differentiated cells from other tissues.

The term plasticity, as used in this report, means that a stem cell from one adult tissue can generate the differentiated cell types of another tissue. At this time, there is no formally accepted name for this phenomenon in the scientific literature. It is variously referred to as "plasticity" [15, 52], "unorthodox differentiation" [10] or "transdifferentiation" [7, 54].

Approaches for Demonstrating Adult Stem Cell Plasticity

To be able to claim that adult stem cells demonstrate plasticity, it is first important to show that a cell population exists in the starting tissue that has the identifying features of stem cells. Then, it is necessary to show that the adult stem cells give rise to cell types that normally occur in a different tissue. Neither of these criteria is easily met. Simply proving the existence of an adult stem cell population in a differentiated tissue is a laborious process. It requires that the candidate stem cells are shown to be self-renewing, and that they can give rise to the differentiated cell types that are characteristic of that tissue.

To show that the adult stem cells can generate other cell types requires them to be tracked in their new environment, whether it is *in vitro* or *in vivo*. In general, this has been accomplished by obtaining the stem cells from a mouse that has been genetically engineered to express a molecular tag in all its cells. It is then necessary to show that the labeled adult stem cells have adopted key structural and biochemical characteristics of the new tissue they are claimed to have generated. Ultimately—and most importantly—it is necessary to demonstrate that the cells can integrate into their new tissue environment, survive in the tissue, and function like the mature cells of the tissue.

In the experiments reported to date, adult stem cells may assume the characteristics of cells that have developed from the same primary germ layer or a different germ layer (see Figure 4.2. Preliminary Evidence of Plasticity Among Nonhuman Adult Stem Cells). For example, many plasticity experiments involve stem cells derived from bone marrow, which is a mesodermal derivative. The bone marrow stem cells may then differentiate into another mesodermally derived tissue such as skeletal muscle [28, 43], cardiac muscle [51, 71] or liver [4, 54, 97].

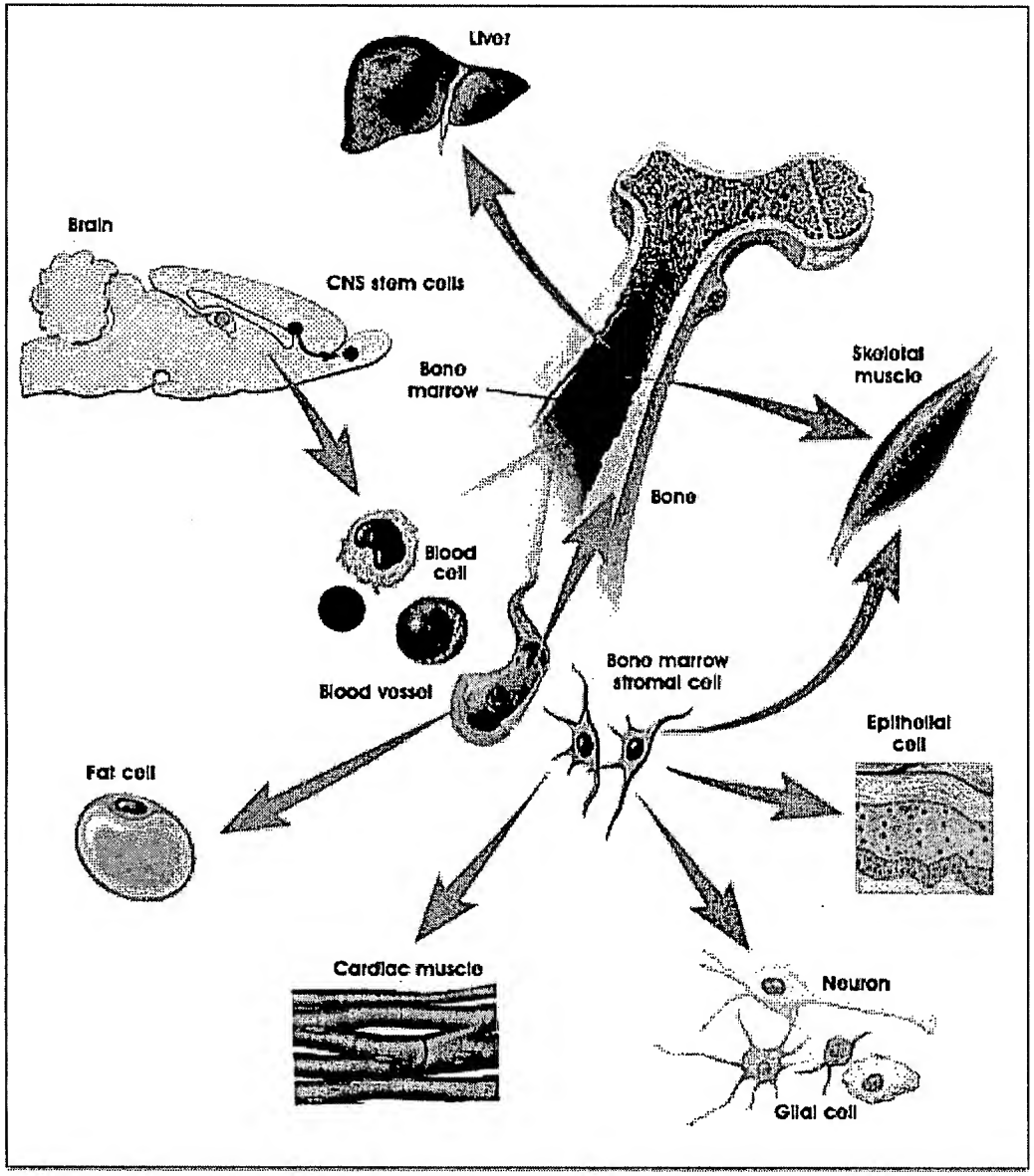

Figure 4.2. Preliminary Evidence of Plasticity Among Nonhuman Adult Stem Cells.

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Alternatively, adult stem cells may differentiate into a tissue that—during normal embryonic development—would arise from a different germ layer. For example, bone marrow-derived cells may differentiate into neural tissue, which is derived from embryonic ectoderm [15, 65]. And—

reciprocally—neural stem cell lines cultured from adult brain tissue may differentiate to form hematopoietic cells [13], or even give rise to many different cell types in a chimeric embryo [17]. In both cases cited above, the cells would be deemed to show plasticity, but in the case of bone marrow stem cells generating brain cells, the finding is less predictable.

In order to study plasticity within and across germ layer lines, the researcher must be sure that he/she is using only one kind of adult stem cell. The vast majority of experiments on plasticity have been conducted with adult stem cells derived either from the bone marrow or the brain. The bone marrow-derived cells are sometimes sorted—using a panel of surface markers—into populations of hematopoietic stem cells or bone marrow stromal cells [46, 54, 71]. The HSCs may be highly purified or partially purified, depending on the conditions used. Another way to separate population of bone marrow cells is by fractionation to yield cells that adhere to a growth substrate (stromal cells) or do not adhere (hematopoietic cells) [28].

To study plasticity of stem cells derived from the brain, the researcher must overcome several problems. **Stem cells** from the central nervous system (CNS), unlike bone marrow cells, do not occur in a single, accessible location. Instead, they are scattered in three places, at least in rodent brain—the tissue around the lateral ventricles in the forebrain, a migratory pathway for the cells that leads from the ventricles to the olfactory bulbs, and the hippocampus. Many of the experiments with CNS stem cells involve the formation of neurospheres, round aggregates of cells that are sometimes clonally derived. But it is not possible to observe cells in the center of a neurosphere, so to study plasticity *in vitro*, the cells are usually dissociated and plated in monolayers. To study plasticity *in vivo*, the cells may be dissociated before injection into the circulatory system of the recipient animal [13], or injected as neurospheres [17].

What is the Evidence for Plasticity?

The differentiated cell types that result from plasticity are usually reported to have the morphological characteristics of the differentiated cells and to display their characteristic surface markers. In reports that transplanted adult stem cells show plasticity *in vivo*, the stem cells typically are shown to have integrated into a mature host tissue and assumed at least some of its characteristics [15, 28, 51, 65, 71]. Many plasticity experiments involve injury to a particular tissue, which is intended to model a particular human disease or injury [13, 54, 71]. However, there is limited evidence to date that such adult stem cells can generate mature, fully functional cells or that the cells have restored lost function *in vivo* [54]. Most of the studies that show the plasticity of adult stem cells involve cells that are derived from the bone marrow [15, 28, 54, 65, 77] or brain [13, 17]. To date, adult stem cells are best characterized in these two tissues, which may account for the greater number of plasticity studies based on bone marrow and brain. Collectively, studies on plasticity suggest that stem cell populations in adult mammals are not fixed entities, and that after exposure to a new environment, they may be able to populate other tissues and possibly differentiate into other cell types.

It is not yet possible to say whether plasticity occurs normally in vivo. Some scientists think it may [14, 64], but as yet there is no evidence to prove it. Also, it is not yet clear to what extent plasticity can occur in experimental settings, and how—or whether—the phenomenon can be harnessed to generate tissues that may be useful for therapeutic transplantation. If the phenomenon of plasticity is to be used as a basis for generating tissue for transplantation, the techniques for doing it will need to be reproducible and reliable (see Chapter 10. Assessing Human Stem Cell Safety). In some cases, debate continues about observations that adult stem cells yield cells of tissue types different than

those from which they were obtained [7, 68].

Experimental Evidence of Adult Stem Cells and Plasticity

Adult Stem Cells of the Nervous System

More than 30 years ago, Altman and Das showed that two regions of the postnatal rat brain, the hippocampus and the olfactory bulb, contain dividing cells that become neurons [5, 6]. Despite these reports, the prevailing view at the time was that nerve cells in the adult brain do not divide. In fact, the notion that stem cells in the adult brain can generate its three major cell types—astrocytes and oligodendrocytes, as well as neurons—was not accepted until far more recently. Within the past five years, a series of studies has shown that stem cells occur in the adult mammalian brain and that these cells can generate its three major cell lineages [35, 48, 63, 66, 90, 96, 104] (see Chapter 8. Rebuilding the Nervous System with Stem Cells).

Today, scientists believe that stem cells in the fetal and adult brain divide and give rise to more stem cells or to several types of precursor cells. Neuronal precursors (also called neuroblasts) divide and give rise to nerve cells (neurons), of which there are many types. Glial precursors give rise to astrocytes or oligodendrocytes. **Astrocytes** are a kind of glial cell, which lend both mechanical and metabolic support for neurons; they make up 70 to 80 percent of the cells of the adult brain. **Oligodendrocytes** make myelin, the fatty material that ensheathes nerve cell axons and speeds nerve transmission. Under normal, *in vivo* conditions, neuronal precursors do not give rise to glial cells, and glial precursors do not give rise to neurons. In contrast, a fetal or adult CNS (central nervous system—the brain and spinal cord) stem cell may give rise to neurons, astrocytes, or oligodendrocytes, depending on the signals it receives and its three-dimensional environment within the brain tissue. There is now widespread consensus that the adult mammalian brain does contain stem cells. However, there is no consensus about how many populations of CNS stem cells exist, how they may be related, and how they function *in vivo*. Because there are no markers currently available to identify the cells *in vivo*, the only method for testing whether a given population of CNS cells contains stem cells is to isolate the cells and manipulate them *in vitro*, a process that may change their intrinsic properties [67].

Despite these barriers, three groups of CNS stem cells have been reported to date. All occur in the adult rodent brain and preliminary evidence indicates they also occur in the adult human brain. One group occupies the brain tissue next to the ventricles, regions known as the ventricular zone and the sub-ventricular zone (see discussion below). The ventricles are spaces in the brain filled with cerebrospinal fluid. During fetal development, the tissue adjacent to the ventricles is a prominent region of actively dividing cells. By adulthood, however, this tissue is much smaller, although it still appears to contain stem cells [70].

A second group of adult CNS stem cells, described in mice but not in humans, occurs in a streak of tissue that connects the lateral ventricle and the olfactory bulb, which receives odor signals from the nose. In rodents, olfactory bulb neurons are constantly being replenished via this pathway [59, 61]. A third possible location for stem cells in adult mouse and human brain occurs in the hippocampus, a part of the brain thought to play a role in the formation of certain kinds of memory [27, 34].

Central Nervous System Stem Cells in the Subventricular Zone. CNS stem cells found in the forebrain that surrounds the lateral ventricles are

heterogeneous and can be distinguished morphologically. Ependymal cells, which are ciliated, line the ventricles. Adjacent to the ependymal cell layer, in a region sometimes designated as the subependymal or subventricular zone, is a mixed cell population that consists of neuroblasts (immature neurons) that migrate to the olfactory bulb, precursor cells, and astrocytes. Some of the cells divide rapidly, while others divide slowly. The astrocyte-like cells can be identified because they contain glial fibrillary acidic protein (GFAP), whereas the ependymal cells stain positive for nestin, which is regarded as a marker of neural stem cells. Which of these cells best qualifies as a CNS stem cell is a matter of debate [76].

A recent report indicates that the astrocytes that occur in the subventricular zone of the rodent brain act as neural stem cells. The cells with astrocyte markers appear to generate neurons *in vivo*, as identified by their expression of specific neuronal markers. The *in vitro* assay to demonstrate that these astrocytes are, in fact, stem cells involves their ability to form neurospheres—groupings of undifferentiated cells that can be dissociated and coaxed to differentiate into neurons or glial cells [25]. Traditionally, these astrocytes have been regarded as differentiated cells, not as stem cells and so their designation as stem cells is not universally accepted.

A series of similar *in vitro* studies based on the formation of neurospheres was used to identify the subependymal zone as a source of adult rodent CNS stem cells. In these experiments, single, candidate stem cells derived from the subependymal zone are induced to give rise to neurospheres in the presence of mitogens—either epidermal growth factor (EGF) or fibroblast growth factor-2 (FGF-2). The neurospheres are dissociated and passaged. As long as a mitogen is present in the culture medium, the cells continue forming neurospheres without differentiating. Some populations of CNS cells are more responsive to EGF, others to FGF [100]. To induce differentiation into neurons or glia, cells are dissociated from the neurospheres and grown on an adherent surface in serum-free medium that contains specific growth factors. Collectively, the studies demonstrate that a population of cells derived from the adult rodent brain can self-renew and differentiate to yield the three major cell types of the CNS cells [41, 69, 74, 102].

Central Nervous System Stem Cells in the Ventricular Zone. Another group of potential CNS stem cells in the adult rodent brain may consist of the ependymal cells themselves [47]. Ependymal cells, which are ciliated, line the lateral ventricles. They have been described as non-dividing cells [24] that function as part of the blood-brain barrier [22]. The suggestion that ependymal cells from the ventricular zone of the adult rodent CNS may be stem cells is therefore unexpected. However, in a recent study, in which two molecular tags—the fluorescent marker DiI, and an adenovirus vector carrying *lacZ* tags—were used to label the ependymal cells that line the entire CNS ventricular system of adult rats, it was shown that these cells could, indeed, act as stem cells. A few days after labeling, fluorescent or $lacZ^+$ cells were observed in the rostral migratory stream (which leads from the lateral ventricle to the olfactory bulb), and then in the olfactory bulb itself. The labeled cells in the olfactory bulb also stained for the neuronal markers βIII tubulin and Map2, which indicated that ependymal cells from the ventricular zone of the adult rat brain had migrated along the rostral migratory stream to generate olfactory bulb neurons *in vivo* [47].

To show that DiI^+ cells were neural stem cells and could generate astrocytes and oligodendrocytes as well as neurons, a neurosphere assay was performed *in vitro*. DiI-labeled cells were dissociated from the ventricular system and cultured in the presence of mitogen to generate neurospheres. Most of the neurospheres were DiI^+; they could self-renew and generate neurons, astrocytes, and oligodendrocytes when induced to differentiate. Single, DiI^+ ependymal cells isolated from the ventricular zone could also generate self-renewing neurospheres and differentiate into neurons and glia.

To show that ependymal cells can also divide *in vivo*, bromodeoxyuridine (BrdU) was administered in the drinking water to rats for a 2- to 6-week period. Bromodeoxyuridine (BrdU) is a **DNA** precursor that is only incorporated into dividing cells. Through a series of experiments, it was shown that ependymal cells divide slowly *in vivo* and give rise to a population of progenitor cells in the subventricular zone [47]. A different pattern of scattered BrdU-labeled cells was observed in the spinal cord, which suggested that ependymal cells along the central canal of the cord occasionally divide and give rise to nearby ependymal cells, but do not migrate away from the canal.

Collectively, the data suggest that CNS ependymal cells in adult rodents can function as stem cells. The cells can self-renew, and most proliferate via asymmetrical division. Many of the CNS ependymal cells are not actively dividing (quiescent), but they can be stimulated to do so *in vitro* (with mitogens) or *in vivo* (in response to injury). After injury, the ependymal cells in the spinal cord only give rise to astrocytes, not to neurons. How and whether ependymal cells from the ventricular zone are related to other candidate populations of CNS stem cells, such as those identified in the hippocampus [34], is not known.

Are ventricular and subventricular zone CNS stem cells the same population? These studies and other leave open the question of whether cells that directly line the ventricles—those in the ventricular zone—or cells that are at least a layer removed from this zone—in the subventricular zone are the same population of CNS stem cells. A new study, based on the finding that they express different genes, confirms earlier reports that the ventricular and subventricular zone cell populations are distinct. The new research utilizes a technique called representational difference analysis, together with cDNA microarray analysis, to monitor the patterns of gene expression in the complex tissue of the developing and postnatal mouse brain. The study revealed the expression of a panel of genes known to be important in CNS development, such as L3-PSP (which encodes a phosphoserine phosphatase important in cell signaling), cyclin D2 (a cell cycle gene), and ERCC-1 (which is important in DNA excision repair). All of these genes in the recent study were expressed in cultured neurospheres, as well as the ventricular zone, the subventricular zone, and a brain area outside those germinal zones. This analysis also revealed the expression of novel genes such as A16F10, which is similar to a gene in an embryonic cancer cell line. A16F10 was expressed in neurospheres and at high levels in the subventricular zone, but not significantly in the ventricular zone. Interestingly, several of the genes identified in cultured neurospheres were also expressed in hematopoietic cells, suggesting that neural stem cells and blood-forming cells may share aspects of their genetic programs or signaling systems [38]. This finding may help explain recent reports that CNS stem cells derived from mouse brain can give rise to hematopoietic cells after injection into irradiated mice [13].

Central Nervous System Stem Cells in the Hippocampus. The hippocampus is one of the oldest parts of the cerebral cortex, in evolutionary terms, and is thought to play an important role in certain forms of memory. The region of the hippocampus in which stem cells apparently exist in mouse and human brains is the subgranular zone of the dentate gyrus. In mice, when BrdU is used to label dividing cells in this region, about 50% of the labeled cells differentiate into cells that appear to be dentate gyrus granule neurons, and 15% become glial cells. The rest of the BrdU-labeled cells do not have a recognizable phenotype [90]. Interestingly, many, if not all the BrdU-labeled cells in the adult rodent hippocampus occur next to blood vessels [33].

In the human dentate gyrus, some BrdU-labeled cells express NeuN, neuron-specific enolase, or calbindin, all of which are neuronal markers. The labeled neuron-like cells resemble dentate gyrus granule cells, in terms of their morphology (as they did in mice). Other BrdU-labeled cells express glial fibrillary acidic protein (GFAP) an astrocyte marker. The study involved autopsy material, obtained with family consent,

from five cancer patients who had been injected with BrdU dissolved in saline prior to their death for diagnostic purposes. The patients ranged in age from 57 to 72 years. The greatest number of BrdU-labeled cells were identified in the oldest patient, suggesting that new neuron formation in the hippocampus can continue late in life [27].

Fetal Central Nervous System Stem Cells. Not surprisingly, fetal stem cells are numerous in fetal tissues, where they are assumed to play an important role in the expansion and differentiation of all tissues of the developing organism. Depending on the developmental stage of an animal, fetal stem cells and precursor cells—which arise from stem cells—may make up the bulk of a tissue. This is certainly true in the brain [48], although it has not been demonstrated experimentally in many tissues.

It may seem obvious that the fetal brain contains stem cells that can generate all the types of neurons in the brain as well as astrocytes and oligodendrocytes, but it was not until fairly recently that the concept was proven experimentally. There has been a long-standing question as to whether or not the same cell type gives rise to both neurons and glia. In studies of the developing rodent brain, it has now been shown that all the major cell types in the fetal brain arise from a common population of progenitor cells [20, 34, 48, 80, 108].

Neural stem cells in the mammalian fetal brain are concentrated in seven major areas: olfactory bulb, ependymal (ventricular) zone of the lateral ventricles (which lie in the forebrain), subventricular zone (next to the ependymal zone), hippocampus, spinal cord, cerebellum (part of the hindbrain), and the cerebral cortex. Their number and pattern of development vary in different species. These cells appear to represent different stem cell populations, rather than a single population of stem cells that is dispersed in multiple sites. The normal development of the brain depends not only on the proliferation and differentiation of these fetal stem cells, but also on a genetically programmed process of selective cell death called apoptosis [76].

Little is known about stem cells in the human fetal brain. In one study, however, investigators derived clonal cell lines from CNS stem cells isolated from the diencephalon and cortex of human fetuses, 10.5 weeks post-conception [103]. The study is unusual, not only because it involves human CNS stem cells obtained from fetal tissue, but also because the cells were used to generate clonal cell lines of CNS stem cells that generated neurons, astrocytes, and oligodendrocytes, as determined on the basis of expressed markers. In a few experiments described as "preliminary," the human CNS stem cells were injected into the brains of immunosuppressed rats where they apparently differentiated into neuron-like cells or glial cells.

In a 1999 study, a serum-free growth medium that included EGF and FGF2 was devised to grow the human fetal CNS stem cells. Although most of the cells died, occasionally, single CNS stem cells survived, divided, and ultimately formed neurospheres after one to two weeks in culture. The neurospheres could be dissociated and individual cells replated. The cells resumed proliferation and formed new neurospheres, thus establishing an *in vitro* system that (like the system established for mouse CNS neurospheres) could be maintained up to 2 years. Depending on the culture conditions, the cells in the neurospheres could be maintained in an undifferentiated dividing state (in the presence of mitogen), or dissociated and induced to differentiate (after the removal of mitogen and the addition of specific growth factors to the culture medium). The differentiated cells consisted mostly of astrocytes (75%), some neurons (13%) and rare oligodendrocytes (1.2%). The neurons generated under these conditions expressed markers indicating they were GABAergic, [the major type of inhibitory neuron in the mammalian CNS responsive to the amino acid neurotransmitter, gammaaminobutyric acid (GABA)]. However, catecholamine-like cells that express

tyrosine hydroxylase (TH, a critical enzyme in the dopamine-synthesis pathway) could be generated, if the culture conditions were altered to include different medium conditioned by a rat glioma line (BB49). Thus, the report indicates that human CNS stem cells obtained from early fetuses can be maintained *in vitro* for a long time without differentiating, induced to differentiate into the three major lineages of the CNS (and possibly two kinds of neurons, GABAergic and TH-positive), and engraft (in rats) in vivo [103].

Central Nervous System Neural Crest Stem Cells. **Neural crest** cells differ markedly from fetal or adult neural stem cells. During fetal development, neural crest cells migrate from the sides of the neural tube as it closes. The cells differentiate into a range of tissues, not all of which are part of the nervous system [56, 57, 91]. Neural crest cells form the sympathetic and parasympathetic components of the peripheral nervous system (PNS), including the network of nerves that innervate the heart and the gut, all the sensory ganglia (groups of neurons that occur in pairs along the dorsal surface of the spinal cord), and **Schwann cells**, which (like oligodendrocytes in the CNS) make myelin in the PNS. The non-neural tissues that arise from the neural crest are diverse. They populate certain hormone-secreting glands—including the adrenal medulla and Type I cells in the carotid body—pigment cells of the skin (melanocytes), cartilage and bone in the face and skull, and connective tissue in many parts of the body [76].

Thus, neural crest cells migrate far more extensively than other fetal neural stem cells during development, form mesenchymal tissues, most of which develop from embryonic mesoderm as well as the components of the CNS and PNS which arises from embryonic ectoderm. This close link, in neural crest development, between ectodermally derived tissues and mesodermally derived tissues accounts in part for the interest in neural crest cells as a kind of stem cell. In fact, neural crest cells meet several criteria of stem cells. They can self-renew (at least in the fetus) and can differentiate into multiple cells types, which include cells derived from two of the three embryonic germ layers [76].

Recent studies indicate that neural crest cells persist late into gestation and can be isolated from E14.5 rat sciatic nerve, a peripheral nerve in the hindlimb. The cells incorporate BrdU, indicating that they are dividing *in vivo*. When transplanted into chick embryos, the rat neural crest cells develop into neurons and glia, an indication of their stem cell-like properties [67]. However, the ability of rat E14.5 neural crest cells taken from sciatic nerve to generate nerve and glial cells in chick is more limited than neural crest cells derived from younger, E10.5 rat embryos. At the earlier stage of development, the neural tube has formed, but neural crest cells have not yet migrated to their final destinations. Neural crest cells from early developmental stages are more sensitive to bone morphogenetic protein 2 (BMP2) signaling, which may help explain their greater differentiation potential [106].

Stem Cells in the Bone Marrow and Blood

The notion that the bone marrow contains stem cells is not new. One population of bone marrow cells, the hematopoietic stem cells (HSCs), is responsible for forming all of the types of blood cells in the body. HSCs were recognized as a stem cells more than 40 years ago [9, 99]. **Bone marrow** stromal cells—a mixed cell population that generates bone, cartilage, fat, fibrous connective tissue, and the reticular network that supports blood cell formation—were described shortly after the discovery of HSCs [30, 32, 73]. The mesenchymal stem cells of the bone marrow also give rise to these tissues, and may constitute the same population of cells as the bone marrow stromal cells [78]. Recently, a population of progenitor cells that differentiates into endothelial cells, a type of cell that lines the blood vessels, was isolated from circulating blood [8] and identified as originating in bone marrow [89]. Whether these endothelial progenitor cells, which resemble the angioblasts that

give rise to blood vessels during embryonic development, represent a bona fide population of adult bone marrow stem cells remains uncertain. Thus, the bone marrow appears to contain three stem cell populations—hematopoietic stem cells, stromal cells, and (possibly) endothelial progenitor cells (see Figure 4.3. Hematopoietic and Stromal Stem Cell **Differentiation**).

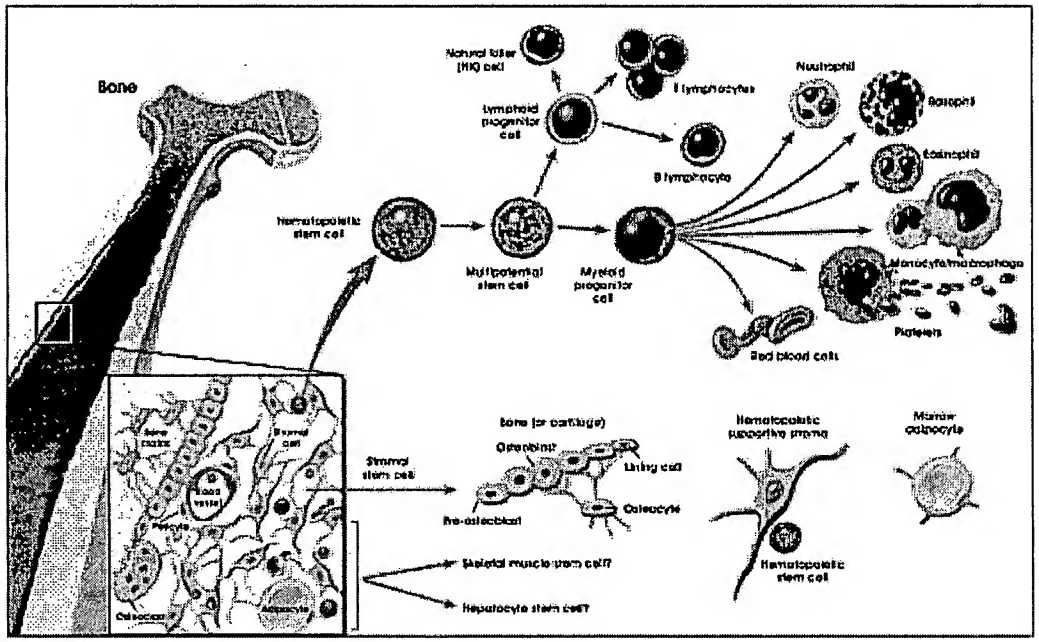

Figure 4.3. Hematopoietic and Stromal Stem Cell Differentiation.

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Two more apparent stem cell types have been reported in circulating blood, but have not been shown to originate from the bone marrow. One population, called pericytes, may be closely related to bone marrow stromal cells, although their origin remains elusive [12]. The second population of blood-born stem cells, which occur in four species of animals tested—guinea pigs, mice, rabbits, and humans—resemble stromal cells in that they can generate bone and fat [53].

Hematopoietic Stem Cells. Of all the cell types in the body, those that survive for the shortest period of time are blood cells and certain kinds of epithelial cells. For example, red blood cells (erythrocytes), which lack a nucleus, live for approximately 120 days in the bloodstream. The life of an animal literally depends on the ability of these and other blood cells to be replenished continuously. This replenishment process occurs largely in the bone marrow, where HSCs reside, divide, and differentiate into all the blood cell types. Both HSCs and differentiated blood cells cycle from the bone marrow to the blood and back again, under the influence of a barrage of secreted factors that regulate cell proliferation, differentiation, and migration (see Chapter 5. Hematopoietic Stem Cells).

HSCs can reconstitute the hematopoietic system of mice that have been subjected to lethal doses of radiation to destroy their own

hematopoietic systems. This test, the rescue of lethally irradiated mice, has become a standard by which other candidate stem cells are measured because it shows, without question, that HSCs can regenerate an entire tissue system—in this case, the blood [9, 99]. HSCs were first proven to be blood-forming stem cells in a series of experiments in mice; similar blood-forming stem cells occur in humans. HSCs are defined by their ability to self-renew and to give rise to all the kinds of blood cells in the body. This means that a single HSC is capable of regenerating the entire hematopoietic system, although this has been demonstrated only a few times in mice [72].

Over the years, many combinations of surface markers have been used to identify, isolate, and purify HSCs derived from bone marrow and blood. **Undifferentiated** HSCs and hematopoietic progenitor cells express c-kit, CD34, and H-2K. These cells usually lack the lineage marker Lin, or express it at very low levels ($Lin^{-/low}$). And for transplant purposes, cells that are $CD34^{+}$ $Thy1^{+}$ Lin^{-} are most likely to contain stem cells and result in engraftment.

Two kinds of HSCs have been defined. Long-term HSCs proliferate for the lifetime of an animal. In young adult mice, an estimated 8 to 10 % of long-term HSCs enter the cell cycle and divide each day. Short-term HSCs proliferate for a limited time, possibly a few months. Long-term HSCs have high levels of telomerase activity. **Telomerase** is an enzyme that helps maintain the length of the ends of chromosomes, called telomeres, by adding on nucleotides. Active telomerase is a characteristic of undifferentiated, dividing cells and cancer cells. Differentiated, human somatic cells do not show telomerase activity. In adult humans, HSCs occur in the bone marrow, blood, liver, and spleen, but are extremely rare in any of these tissues. In mice, only 1 in 10,000 to 15,000 bone marrow cells is a long-term HSC [105].

Short-term HSCs differentiate into lymphoid and myeloid precursors, the two classes of precursors for the two major lineages of blood cells. **Lymphoid** precursors differentiate into **T cells**, **B cells**, and natural killer cells. The mechanisms and pathways that lead to their differentiation are still being investigated [1, 2]. **Myeloid** precursors differentiate into monocytes and macrophages, neutrophils, eosinophils, basophils, megakaryocytes, and erythrocytes [3]. ***In vivo***, bone marrow HSCs differentiate into mature, specialized blood cells that cycle constantly from the bone marrow to the blood, and back to the bone marrow [26]. A recent study showed that short-term HSCs are a heterogeneous population that differ significantly in terms of their ability to self-renew and repopulate the hematopoietic system [42].

Attempts to induce HSC to proliferate *in vitro*—on many substrates, including those intended to mimic conditions in the stroma—have frustrated scientists for many years. Although HSCs proliferate readily *in vivo*, they usually differentiate or die *in vitro* [26]. Thus, much of the research on HSCs has been focused on understanding the factors, cell-cell interactions, and cell-matrix interactions that control their proliferation and differentiation *in vivo*, with the hope that similar conditions could be replicated *in vitro*. Many of the soluble factors that regulate HSC differentiation *in vivo* are cytokines, which are made by different cell types and are then concentrated in the bone marrow by the extracellular matrix of stromal cells—the sites of blood formation [45, 107]. Two of the most-studied cytokines are granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-3 (IL-3) [40, 81].

Also important to HSC proliferation and differentiation are interactions of the cells with adhesion molecules in the extracellular matrix of the bone marrow stroma [83, 101, 110].

Bone Marrow Stromal Cells. Bone marrow (BM) stromal cells have long been recognized for playing an important role in the differentiation of

mature blood cells from HSCs (see Figure 4.3. Hematopoietic and Stromal Stem Cell Differentiation). But stromal cells also have other important functions [30, 31]. In addition to providing the physical environment in which HSCs differentiate, BM stromal cells generate cartilage, bone, and fat. Whether stromal cells are best classified as stem cells or progenitor cells for these tissues is still in question. There is also a question as to whether BM stromal cells and so-called mesenchymal stem cells are the same population [78].

BM stromal cells have many features that distinguish them from HSCs. The two cell types are easy to separate *in vitro*. When bone marrow is dissociated, and the mixture of cells it contains is plated at low density, the stromal cells adhere to the surface of the culture dish, and the HSCs do not. Given specific *in vitro* conditions, BM stromal cells form colonies from a single cell called the colony forming unit-F (CFU-F). These colonies may then differentiate as adipocytes or myelosupportive stroma, a clonal assay that indicates the stem cell-like nature of stromal cells. Unlike HSCs, which do not divide *in vitro* (or proliferate only to a limited extent), BM stromal cells can proliferate for up to 35 population doublings *in vitro* [16]. They grow rapidly under the influence of such mitogens as platelet-derived growth factor (**PDGF**), epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), and insulin-like growth factor-1 (IGF-1) [12].

To date, it has not been possible to isolate a population of pure stromal cells from bone marrow. Panels of markers used to identify the cells include receptors for certain cytokines (interleukin-1, 3, 4, 6, and 7) receptors for proteins in the extracellular matrix, (ICAM-1 and 2, VCAM-1, the alpha-1, 2, and 3 integrins, and the beta-1, 2, 3 and 4 integrins), etc. [64]. Despite the use of these markers and another stromal cell marker called Stro-1, the origin and specific identity of stromal cells have remained elusive. Like HSCs, BM stromal cells arise from embryonic mesoderm during development, although no specific precursor or stem cell for stromal cells has been isolated and identified. One theory about their origin is that a common kind of progenitor cell—perhaps a primordial endothelial cell that lines embryonic blood vessels—gives rise to both HSCs and to mesodermal precursors. The latter may then differentiate into myogenic precursors (the satellite cells that are thought to function as stem cells in skeletal muscle), and the BM stromal cells [10].

In vivo, the differentiation of stromal cells into fat and bone is not straightforward. Bone marrow adipocytes and myelosupportive stromal cells—both of which are derived from BM stromal cells—may be regarded as interchangeable phenotypes [10, 11]. **Adipocytes** do not develop until postnatal life, as the bones enlarge and the marrow space increases to accommodate enhanced hematopoiesis. When the skeleton stops growing, and the mass of HSCs decreases in a normal, age-dependent fashion, BM stromal cells differentiate into adipocytes, which fill the extra space. New bone formation is obviously greater during skeletal growth, although bone "turns over" throughout life. Bone forming cells are osteoblasts, but their relationship to BM stromal cells is not clear. New trabecular bone, which is the inner region of bone next to the marrow, could logically develop from the action of BM stromal cells. But the outside surface of bone also turns over, as does bone next to the Haversian system (small canals that form concentric rings within bone). And neither of these surfaces is in contact with BM stromal cells [10, 11].

Adult Stem Cells in Other Tissues

It is often difficult—if not impossible—to distinguish adult, tissue-specific stem cells from progenitor cells. With that caveat in mind, the following summary identifies reports of stem cells in various adult tissues.

Endothelial Progenitor Cells. Endothelial cells line the inner surfaces of blood vessels throughout the body, and it has been difficult to identify specific endothelial stem cells in either the embryonic or the adult mammal. During embryonic development, just after gastrulation, a kind of cell called the hemangioblast, which is derived from mesoderm, is presumed to be the precursor of both the hematopoietic and endothelial cell lineages. The embryonic vasculature formed at this stage is transient and consists of blood islands in the yolk sac. But hemangioblasts, per se, have not been isolated from the embryo and their existence remains in question. The process of forming new blood vessels in the embryo is called vasculogenesis. In the adult, the process of forming blood vessels from pre-existing blood vessels is called angiogenesis [50].

Evidence that hemangioblasts do exist comes from studies of mouse embryonic stem cells that are directed to differentiate *in vitro*. These studies have shown that a precursor cell derived from mouse **ES** cells that express Flk-1 [the receptor for vascular endothelial growth factor (**VEGF**) in mice] can give rise to both blood cells and blood vessel cells [88, 109]. Both VEGF and fibroblast growth factor-2 (FGF-2) play critical roles in endothelial cell differentiation *in vivo* [79].

Several recent reports indicate that the bone marrow contains cells that can give rise to new blood vessels in tissues that are ischemic (damaged due to the deprivation of blood and oxygen) [8, 29, 49, 94]. But it is unclear from these studies what cell type(s) in the bone marrow induced angiogenesis. In a study which sought to address that question, researchers found that adult human bone marrow contains cells that resemble embryonic hemangioblasts, and may therefore be called endothelial stem cells.

In more recent experiments, human bone marrow-derived cells were injected into the tail veins of rats with induced cardiac ischemia. The human cells migrated to the rat heart where they generated new blood vessels in the infarcted muscle (a process akin to vasculogenesis), and also induced angiogenesis. The candidate endothelial stem cells are $CD34^+$(a marker for HSCs), and they express the **transcription factor** GATA-2 [51]. A similar study using transgenic mice that express the gene for enhanced green fluorescent protein (which allows the cells to be tracked), showed that bone-marrow-derived cells could repopulate an area of infarcted heart muscle in mice, and generate not only blood vessels, but also cardiomyocytes that integrated into the host tissue [71] (see Chapter 9. Can Stem Cells Repair a Damaged Heart?).

And, in a series of experiments in adult mammals, progenitor endothelial cells were isolated from peripheral blood (of mice and humans) by using antibodies against CD34 and Flk-1, the receptor for VEGF. The cells were mononuclear blood cells (meaning they have a nucleus) and are referred to as MB^{CD34+} cells and MB^{Flk1+} cells. When plated in tissue-culture dishes, the cells attached to the substrate, became spindle-shaped, and formed tube-like structures that resemble blood vessels. When transplanted into mice of the same species (autologous transplants) with induced ischemia in one limb, the MB^{CD34+} cells promoted the formation of new blood vessels [8]. Although the adult MB^{CD34+} and MB^{Flk1+} cells function in some ways like stem cells, they are usually regarded as progenitor cells.

Skeletal Muscle Stem Cells. Skeletal muscle, like the cardiac muscle of the heart and the smooth muscle in the walls of blood vessels, the digestive system, and the respiratory system, is derived from embryonic mesoderm. To date, at least three populations of skeletal muscle stem cells have been identified: satellite cells, cells in the wall of the dorsal aorta, and so-called "side population" cells.

Satellite cells in skeletal muscle were identified 40 years ago in frogs by electron microscopy [62], and thereafter in mammals [84]. Satellite cells occur on the surface of the basal lamina of a mature muscle cell, or myofiber. In adult mammals, satellite cells mediate muscle growth [85]. Although satellite cells are normally non-dividing, they can be triggered to proliferate as a result of injury, or weight-bearing exercise. Under either of these circumstances, muscle satellite cells give rise to myogenic precursor cells, which then differentiate into the myofibrils that typify skeletal muscle. A group of transcription factors called myogenic regulatory factors (MRFs) play important roles in these differentiation events. The so-called primary MRFs, MyoD and Myf5, help regulate myoblast formation during embryogenesis. The secondary MRFs, myogenin and MRF4, regulate the terminal differentiation of myofibrils [86].

With regard to satellite cells, scientists have been addressing two questions. Are skeletal muscle satellite cells true adult stem cells or are they instead precursor cells? Are satellite cells the only cell type that can regenerate skeletal muscle. For example, a recent report indicates that muscle stem cells may also occur in the dorsal aorta of mouse embryos, and constitute a cell type that gives rise both to muscle satellite cells and endothelial cells. Whether the dorsal aorta cells meet the criteria of a self-renewing muscle stem cell is a matter of debate [21].

Another report indicates that a different kind of stem cell, called an **SP** cell, can also regenerate skeletal muscle may be present in muscle and bone marrow. SP stands for a side population of cells that can be separated by fluorescence-activated cell sorting analysis. Intravenously injecting these muscle-derived stem cells restored the expression of dystrophin in mdx mice. Dystrophin is the protein that is defective in people with Duchenne's muscular dystrophy; mdx mice provide a model for the human disease. Dystrophin expression in the SP cell-treated mice was lower than would be needed for clinical benefit. Injection of bone marrow- or muscle-derived SP cells into the dystrophic muscle of the mice yielded equivocal results that the transplanted cells had integrated into the host tissue. The authors conclude that a similar population of SP stem cells can be derived from either adult mouse bone marrow or skeletal muscle, and suggest "there may be some direct relationship between bone marrow-derived stem cells and other tissue- or organ-specific cells" [43]. Thus, stem cell or progenitor cell types from various mesodermally-derived tissues may be able to generate skeletal muscle.

Epithelial Cell Precursors in the Skin and Digestive System. Epithelial cells, which constitute 60 percent of the differentiated cells in the body are responsible for covering the internal and external surfaces of the body, including the lining of vessels and other cavities. The epithelial cells in skin and the digestive tract are replaced constantly. Other epithelial cell populations—in the ducts of the liver or pancreas, for example—turn over more slowly. The cell population that renews the epithelium of the small intestine occurs in the intestinal crypts, deep invaginations in the lining of the gut. The crypt cells are often regarded as stem cells; one of them can give rise to an organized cluster of cells called a structural-proliferative unit [93].

The skin of mammals contains at least three populations of epithelial cells: epidermal cells, hair follicle cells, and glandular epithelial cells, such as those that make up the sweat glands. The replacement patterns for epithelial cells in these three compartments differ, and in all the compartments, a stem cell population has been postulated. For example, stem cells in the bulge region of the hair follicle appear to give rise to multiple cell types. Their progeny can migrate down to the base of the follicle where they become matrix cells, which may then give rise to different cell types in the hair follicle, of which there are seven [39]. The bulge stem cells of the follicle may also give rise to the epidermis of the skin [95].

Another population of stem cells in skin occurs in the basal layer of the epidermis. These stem cells proliferate in the basal region, and then differentiate as they move toward the outer surface of the skin. The keratinocytes in the outermost layer lack nuclei and act as a protective barrier. A dividing skin stem cell can divide asymmetrically to produce two kinds of daughter cells. One is another self-renewing stem cell. The second kind of daughter cell is an intermediate precursor cell which is then committed to replicate a few times before differentiating into keratinocytes. Self-renewing stem cells can be distinguished from this intermediate precusor cell by their higher level of β1 integrin expression, which signals keratinocytes to proliferate via a mitogen-activated protein (MAP) kinase [112]. Other signaling pathways include that triggered by -catenin, which helps maintain the stem-cell state [111], and the pathway regulated by the oncoprotein c-Myc, which triggers stem cells to give rise to transit amplifying cells [36].

Stem Cells in the Pancreas and Liver. The status of stem cells in the adult pancreas and liver is unclear. During embryonic development, both tissues arise from endoderm. A recent study indicates that a single precursor cell derived from embryonic endoderm may generate both the ventral pancreas and the liver [23]. In adult mammals, however, both the pancreas and the liver contain multiple kinds of differentiated cells that may be repopulated or regenerated by multiple types of stem cells. In the pancreas, endocrine (hormone-producing) cells occur in the islets of Langerhans. They include the beta cells (which produce insulin), the alpha cells (which secrete glucagon), and cells that release the peptide hormones somatostatin and pancreatic polypeptide. Stem cells in the adult pancreas are postulated to occur in the pancreatic ducts or in the islets themselves. Several recent reports indicate that stem cells that express nestin—which is usually regarded as a marker of neural stem cells—can generate all of the cell types in the islets [60, 113] (see Chapter 7. Stem Cells and Diabetes).

The identity of stem cells that can repopulate the liver of adult mammals is also in question. Recent studies in rodents indicate that HSCs (derived from mesoderm) may be able to home to liver after it is damaged, and demonstrate plasticity in becoming into hepatocytes (usually derived from endoderm) [54, 77, 97]. But the question remains as to whether cells from the bone marrow normally generate hepatocytes *in vivo.* It is not known whether this kind of plasticity occurs without severe damage to the liver or whether HSCs from the bone marrow generate oval cells of the liver [18]. Although hepatic oval cells exist in the liver, it is not clear whether they actually generate new hepatocytes [87, 98]. Oval cells may arise from the portal tracts in liver and may give rise to either hepatocytes [19, 55] and to the epithelium of the bile ducts [37, 92]. Indeed, hepatocytes themselves, may be responsible for the well-know regenerative capacity of liver.

Summary

- Adult stem cells can proliferate without differentiating for a long period (a characteristic referred to as long-term self-renewal), and they can give rise to mature cell types that have characteristic shapes and specialized functions.
- Some adult stem cells have the capability to differentiate into tissues other than the ones from which they originated; this is referred to as plasticity.
- Adult stem cells are rare. Often they are difficult to identify and their origins are not known. Current methods for characterizing adult stem cells are dependent on determining cell surface markers and observations about their differentiation patterns in test tubes and culture dishes.

- To date, published scientific literature indicates that adult stem cells have been derived from brain, bone marrow, peripheral blood, dental pulp, spinal cord, blood vessels, skeletal muscle, epithelia of the skin and digestive system, cornea, retina, liver, and pancreas; thus, adult stem cells have been found in tissues that develop from all three embryonic germ layers.
- **Hematopoietic stem cells** from bone marrow are the most studied and used for clinical applications in restoring various blood and immune components to the bone marrow via transplantation. There are at least two other populations of adult stem cells that have been identified from bone marrow and blood.
- Several populations of adult stem cells have been identified in the brain, particularly the hippocampus. Their function is unknown. Proliferation and differentiation of brain stem cells are influenced by various growth factors.
- There are now several reports of adult stem cells in other tissues (muscle, blood, and fat) that demonstrate plasticity. Very few published research reports on plasticity of adult stem cells have, however, included clonality studies. That is, there is limited evidence that a single adult stem cell or genetically identical line of adult stem cells demonstrates plasticity.
- Rarely have experiments that claim plasticity demonstrated that the adult stem cells have generated mature, fully functional cells or that the cells have restored lost function *in vivo*.

What Do We Need to Know About Adult Stem Cells?

- What are the sources of adult stem cells in the body? Are they "leftover" embryonic stem cells, or do they arise in some other way? And if the latter is true—which seems to be the case—exactly how do adult stem cells arise, and why do they remain in an undifferentiated state, when all the cells around them have differentiated?
- Is it possible to manipulate adult stem cells to increase their ability to proliferate *in vitro*, so that adult stem cells can be used as a sufficient source of tissue for transplants?
- How many kinds of adult stem cells exist, and in which tissues do they exist? Evidence is accumulating that, although they occur in small numbers, adult stem cells are present in many differentiated tissues.
- What is the best evidence that adult stem cells show plasticity and generate cell types of other tissues?
- Is it possible to manipulate adult stem cells to increase their ability to proliferate *in vitro* so that adult stem cells can be used as a sufficient source of tissue for transplants?
- Is there a universal stem cell? An emerging concept is that, in adult mammals, there may be a population of "universal" stem cells. Although largely theoretical, the concept has some experimental basis. A candidate, universal adult stem cell may be one that circulates in the blood stream, can escape from the blood, and populate various adult tissues. In more than one experimental system, researchers have noted that dividing cells in adult tissues often appear near a blood vessel, such as candidate stem cells in the hippocampus, a region of the brain [75].

- Do adult stem cells exhibit plasticity as a normal event *in vivo*? If so, is this true of all adult stem cells? What are the signals that regulate the proliferation and differentiation of stem cells that demonstrate plasticity?

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FIRSTGOV

Living Longer and Loving It! issue 8

Science in the Spotlight

Body, Heal Thyself: Science Fiction or Reality?

We don't think it's miraculous when a cut finger heals on its own, or a sprained ankle becomes good as new over a matter of weeks. But what if arthritis or heart disease could be treated or prevented the same way — by using the body's natural healing powers? Now are we talking miraculous?

Not according to William Haseltine, CEO of Human Genome Sciences Inc., and the leading pioneer in the field of regenerative medicine. This emerging area involves harnessing the chemical signals the body uses to trigger cell repair and replacement.

"When we know, in effect, what our cells know, health care will be revolutionized, giving birth to regenerative medicine — ultimately including the prolongation of life by regenerating our aging bodies with younger cells," Dr. Haseltine told the New York Times in a November 2000 article.

Cells communicate with one another; they "discuss" when to make certain proteins, where the proteins should go, and what should happen when they reach their destinations. Dr. Haseltine and his colleagues at Human Genome Sciences claim to have identified the components of this amazing communication system - or the words used in this cellular "language" - and are in the process of discovering what each word might mean.

If Dr. Haseltine and his company can translate the cellular language, the possibilities for humanity are endless. For example, a protein called B-lymphocyte stimulator will be tested on people with defective immune systems, in hopes of boosting their levels of a type of white blood cell. A drug to block this protein could prove useful for people with certain autoimmune diseases, such as lupus and rheumatoid arthritis. Other proteins could be used to jump-start wound healing, replace diseased tissue,

EXHIBIT "B"

combat cancer, and just about anything else you can think of.

Regenerative medicine uses genes, proteins, and antibodies as medicines. Instead of getting a drug, a patient might receive a growth factor, gene therapy, hormone treatment, antibody treatment or other treatment. According to Dr. Haseltine, these types of treatments will make up half of all therapies in the next 20 years.

Regenerative medicine also involves using human cells to rebuild organs, either by injection into diseased tissues or by constructing new healthy organs outside the body as replacements. The latter concept, called autotransplantation, is under study by Dr. Haseltine and others; one he believes will soon be reality.

Stem cells are a mainstay of regenerative medicine. These cells are the "blank slates" of the body — they haven't committed to becoming a skin cell, heart cell or kidney cell. This type of research has focused on two primary areas: adult stem cells and human embryonic stem cells. Adult pluripotent stem cells have the potential to become many different types of cells. Human embryonic pluripotent stem cells are even more powerful: they are totipotent, capable of becoming any type of mature human cell.

Stem cells cannot only be coaxed down a certain life path (to become a heart muscle cell, for example, or a liver cell), they also can latch on to tissue in the body and become that type of tissue. Depending on how they are cultured, a type of adult stem cell called a bone marrow stromal cell, for example, can develop into bone cells or cartilage cells in the laboratory. Researchers believe that if these cells are given to people undergoing bone marrow transplants, they may help the bone marrow recover faster and thus make people healthier faster too.

Dr. Haseltine predicts that in the future regenerative medicine will be able to trigger the body to do what's necessary — eliminate a tumor, heal a wound, or re-grow lost neurons. We will be able to grow any tissue, regulate any cell signal and rebuild any organ. It may sound like impossible science fiction, but the body already does miraculous things on its own. Dr. Haseltine, and others, are just trying to understand how so that we can harness this incredible ability to self-heal and regenerate.

  

Winter 2001 Home *Email this article to a friend* *Print this article*

Archives

Fall 2003

The Best Disney Movie Yet

No Disney movie has a better story than this one. On August 2, 2003 a very special wedding took place between Kathryn Muldowney and Michael Powers at an idyllic setting in Port Jefferson on Long Island.

The wedding was like most: a beautiful bride, a handsome groom, luscious flowers, and family and friends gathered to join them in the celebration. It was the way they handled the wedding gifts and their honeymoon that was very different.

Kathryn and Michael decided to make Disney World their honeymoon destination. The trip was not for themselves but for Kathryn's nephew and Michael's sons. Kathryn's nephew, Jonathan Pultz, has Erythropoietic Protoporphyria (EPP), and is, therefore, not able to enjoy the same activities as most youngsters because of his photosensitivity. Since Disney World is as fun at night as it is in the daytime, Johnathan could join Michael's sons and have as much pleasure there as any other twelve-year-old boy. So while all the thousands of bride and grooms travel this summer to destinations more geared for adults than the Disney World theme park, Kathryn and Michael will be sailing through the likes of "Pirates of the Caribbean" with their very happy boys.

To add to the goodness of their story, Kathryn and Michael asked the wedding guests to forego wedding gifts and make donations to the APF instead. Imagine our surprise when Diane Pultz, Jonathan's mom, contacted the office and told us that the couple was considering such a generous offer to help kids, like

EXHIBIT "C"

Jonathan, with EPP. During the course of their conversation, Desiree provided Diane with information about the services and programs of the APF and explained that the couple could designate where they would like to place the donations. Shortly thereafter, the APF began to receive donations in honor of Kathryn and Michael's marriage from their family and friends. Every gift was particularly touching in light of the kindness and unselfishness behind each generous donation.

Thank you to the Pultz, Powers and Muldowney families and to their many friends, who have shared in the ultimate experience of "It is better to give than to receive." We want to add a special thanks to Ed Muldowney, Kathryn's dad, for his support and for setting such a compassionate example in life for Kathryn to follow.

With such unpleasant news all around us, it is a joy to hear such an extraordinary loving story.

If you or your family members have had an experience that would interest our readers, please contact Desiree Lyon at the APF office or lyonapf@aol.com. Our members often write that they enjoy reading about other members so we would appreciate the opportunity to provide space for you to encourage others with your experience. Also, it adds to the story if you can provide a photograph. As they say, a photograph is worth a thousand words. You can either email a digital photo or send a photo through the regular mail. Both are appreciated.

What You Wanted To Know About Stem Cells

Stem cells are a pretty popular subject of discussion these days. It is important for people to know the basics about them because these cells are potentially important in the cure of EPP and other genetic diseases. Stem cells are unspecialized cells which have the ability to reproduce themselves without limit, and also to give rise to specialized (differentiated) cells, such as heart or blood or muscle or brain cells, which could be used to make replacements for diseased tissues or organs, when the stem cells are grown in the presence of specific chemical nutrients. Stem cells normally are present in very young embryos, older embryos and fetuses, umbilical cords at birth, and in children and adults.

Embryonic stem cells

It is a fact of embryology that people start their lives as one cell, called the zygote-this is the cell which forms when the oocyte (egg cell) of the mother joins with the sperm cell of the father. This is the first cell of each of us, because it contains our unique set of chromosomes, half of which were inherited from our moms and half from our dads. The zygote starts to divide into two, then four cells. By the third day of life, 12 to 15 cells have formed, making a solid ball of cells: at this stage, the growing young human is called a morula. On the fourth day of life, the morula enters the mother's uterus. Soon a fluid-filled space forms in the morula - separates the little ball of cell into two parts: 1) a thin outer layer of cells called the trophoblast, which gives rise to the baby's part of the placenta and its associated membranes, and 2) a little ball of cells located inside the trophoblast and surrounded by the fluid, called the inner cell mass - these cells are the embryonic stem cells. The embryonic stem cells go on to form the entire embryo - every kind of cell and tissue in the growing little human (and eventually, with further growth, in the fetus, child and adult). At this stage the growing human is called a blastocyst.

This is how embryonic stem cells are formed in the "usual" way. You have heard of "in vitro fertilization" (IVF), a technique, which helps couples having problems conceiving a baby. In IVF, oocytes and sperm are mixed in a petri dish, which contains a special nutrient solution, and they join in the dish to form a zygote, just as they would join in the mother's uterus. The zygote starts to divide as it would in the uterus: the early development of the embryo (the generic term for a growing human from fertilization until the end of the 8th week of life - from then until birth we are called a fetus) is the same in a petri dish as it

is in the mom's uterus. Usually, the embryos are allowed to grow for about 3 days, checked to make sure they are healthy and then either implanted in the prospective mom's uterus, or frozen in a special protective solution for future use, in case the first implantation does not result in pregnancy. Occasionally the embryos are cultured to the blastocyst stage, and then are frozen. Implantation of thawed 3 day old embryos and blastocysts have resulted in successful pregnancies.

People who want to do research on embryonic stem cells want to obtain "extra" frozen embryos and blastocysts from IVF clinics and either culture the 3-day old ones to the blastocyst stage, or work directly with the blastocysts, which had been frozen. To obtain the inner cell mass cells, i.e. embryonic stem cells, the blastocysts are put in a special solution containing specific antibodies, which cause the trophoblast cells to dissolve, and the inner cell mass cells are released. The stem cells are then washed and cultured in appropriate media for various studies, hopefully to get them to form specialized cells and tissues.

It is important for people to realize that the process of opening up the trophoblast and obtaining the embryonic stem cells kills the growing young human being. Unfortunately, in addition to this serious ethical problem, of killing one very young member of our own human species, there are also some medical problems associated with the use of embryonic stem cells. The same problems if immunological rejection, graft-versus-host disease, etc., that a patient gets from receiving an organ from an organ donor who is not one's identical twin will occur with cells or tissues made from embryonic stem cells, because the parents of the embryos are not related to the patient who will receive the cells and tissues made from those embryonic stem cells. Additionally, embryonic stem cells have the tendency of forming teratomas, which are tumors made up of several kinds of differentiated cells, which often form when the stem cells are implanted into different organs, as has been found in animal studies.

Embryonic stem cells from cloned embryos
Scientists thought that the problems of immunological rejection could be avoided by making cloned embryos and harvesting their stem cells and using these to make the cells and tissues a patient needs to treat his/her disease - they call this "theraputic cloning". Cloning is done by taking an oocyte from a female donor and removing its nucleus. Then, a somatic cell (a body cell, not an oocyte or sperm cell) is obtained from the patient to be treated (or cloned), and its nucleus is removed and is placed into that oocyte. The oocyte with its new nucleus, which has all 46 chromosomes, is the first cell, the zygote, of the cloned individual. This zygote is then stimulated to start its growth/development. The cloned zygote's development is the same as that of a zygote produced by the union of egg and sperm by either sexual reproduction (the usual way) or by in-vitro fertilization (VF).

However, stem cells from cloned embryos would still lead to some immunological rejection problems, because a crucial part of all cloned cells, the mitochondria, which direct certain aspects of cell metabolism, are all derived from the mitochondria from the oocyte, not from the genes of the donor nucleus, and thus could trigger rejection. Also, teratoma formation could occur. Additionally, since many mutations occur in the early embryo in the first few days of life, a cloned embryo would not be exempt from developing these mutations, which would be transmitted to the inner mass cells (i.e. the embryonic stem cells). In normal development on the uterus, the majority of these defective embryos would be eliminated because they can't develop to implantation into the mother's uterus and develop beyond the early stages of life, but when development is stopped at 5 to 7 days by the cloning process, these early mutations are not eliminated. There is the possibility that these mutations may cause problems in the differentiated cells developed from the defective clone's embryonic stem cells. Also, reprogramming and imprinting errors of the patient's chromosomes developed in the early embryo would probably remain in the stem cells developed from that embryo, and may lead to future problems, perhaps malignancies, in the cells and tissues developed from them. It is important to remember that destroying a cloned embryo to get its stem cells would also be killing a little growing human being.

Ethical problems aside, we have to remember that there is no guarantee that we will be able to master the process of directing embryonic stem cells from either cloned embryos or IVF embryos into developing into the kinds of differentiated cells or tissues we need for therapy without causing harm to the recipient of these cells or tissues: we are years away from achieving the goal of safe and effective embryonic stem cell therapy.

Older embryo and fetal stem cells
Stem cells are also obtained by isolating cells from an area of the body of 5-8 week embryos and 9 week-old fetuses called the germinal ridge: these cells are called primordial germ cells and are the cells which would eventually differentiate into oocytes or sperm, depending on the sex of the embryo from which they are obtained. These cells are diploid (i.e. have 46 chromosomes), as they have not yet undergone the "meiotic" division, which they need to undergo to become mature haploid (I.e have 23 chromosomes) oocytes or sperm. The embryos and young fetuses, which are usually obtained from abortions, are autopsied, and their germinal ridges are removed and the cells from there are isolated and grown in special tissue culture media. It is also possible to obtain such stem cells from embryos and fetuses, who have died due to miscarriage or premature birth. However, specialized cells and tissues formed from these stem cells would lead to the same immunological rejection problems as would embryonic stem cells. They also form teratomas, as was found in a study with human patients where these cells were injected into the brain—teratomas formed and had to be surgically removed. So, these kinds of stem cells also present problems.

Umbilical cord stem cells
These are harvested from umbilical cords and placentas at the time of birth. Many parents are having their newborn's umbilical cord stem cells harvested and stored in cell banks (similar to blood banks) for future use, if the need for a bone marrow transplant ever arises. These cells will not form teratomas, but would cause rejection problems if used by others besides the child from whose umbilical cord they come. Much work is being done on them, but it is not yet known how many types of organs or tissues they could form.

Adult (i.e. post-natal) stem cells
Children and adults have stem cells in their bodies. Adult stem cells are obtained from bone marrow donations or organ biopsies: these procedures do not permanently harm the donor, though they may cause a bit of local pain when they are performed. Several organs, such as pancreas, liver and brain, have been found to have stem cells specific to them and there are also certain other kinds of stem cells which can make a variety of different tissues, which would be very useful for treating disease: there are many reports about this in medical and scientific journals. One of the more versatile adult stem cells is the bone marrow stromal cell, which can give rise to many different kinds of specialized cells, including liver cells (hepatocytes), brain cells (neurons), dendritic cells (immune system cells), bone cells, fat cells and cartilage cells. Another very exciting example of an adult stem cell is one also found in the bone marrow and called multipotent adult progenitor cells (MAPCs) which can be made to differentiate into cells of all three embryonic layers - endoderm, mesoderm and ectoderm, including the various kinds of blood cells: the ability to do this makes these cells as versatile as embryonic stem cells. The MAPCs are found in human bone marrow, as well as in mouse bone marrow. They do not form teratomas, and would not cause immunological rejection, as they would be isolated from the bone marrow of the patient who would receive the cells or tissues made from them. Another potentially exciting new stem cell has been found in perlheral blood, which can be differentiated into endothelial cells, nerve cells and liver cells and certain kinds of blood cells, but it is not yet known if these can develop into red blood cells, which they would have to do to be useful for EPP treatments. The advantage of these cells would be that patients would not have to undergo bone marrow punctures, which can be somewhat painful—drawing blood from a vein is much less so.

From our survey of stem cells, it would appear that the best and safest ones to use would be adult stem cells. For the treatment of genetic diseases, the patients' own stem cells would be obtained and the normal

version of the gene defective in the particular disease would then be added to the stem cell via a harmless carrier called a vector. In the case of EPP and congenital porphyria, which are both bone-marrow based diseases, their respective normal version of the defective gene would be added to either bone-marrow or peripheral blood stem cells or MAPC cells, and in the case of the liver-based porphyrias, their respective normal gene could be added to either bone marrow stromal cells or liver stem cells or maybe even to MAPC cells. Remember, it will be quite a few years before these therapies will be ready for use in people - there is still much safety and toxicity studies to be done in animals. The best thing for you to do is to stay in contact with APF and the EPPREF (the latter for EPP people)—These groups will be the first to know when studies in porphyria patients will be ready to accept patients.

Reprinted from EPPREF NEWS, Issue #35, with slight modifications. Thanks to Dr. Michelene Mathews-oth.

Paula

Paula, a book by Isabel Allende, has been on bookshelves for years and is still a must read. It is the noted author's account of her 28-year-old daughter, Paula, who went into a coma in Madrid after an attack of acute intermittent porphyria. *Paula* is a deeply moving tale of Allende's own life, which she wrote as a gift for Paula's recovery. It is also a vivid portrait of Chile from postcolonial propriety to Pinochet's oppression. The tone of *Paula* changes when Allende realizes that Paula can never be revived and brings her home to California to live her last days surrounded by her loving family. In the remainder of the book, Allende speaks not to Paula but about Paula and gives the reader insight into what it takes to bear a great loss.

A Collaborative Effort

A few years ago, Dr. Harry Dailey, Director of the University of Georgia's Biomedical and Health Science Center, and his colleague, Dr. Peter Meissner, who is the director of the internationally recognized Porphyria Research Unit at UCT, the University of Cape Town and the leading researcher on porphyria in South Africa, began an important collaborative effort for the benefit of Porphyria patients.

An integral part of Dr. Dailey's research is to understand the specific nature of variegate porphyria (VP) and erythropoietic protoporphyria (EPP) at both a biochemical and cellular level. Half a world away, Dr. Peter Meissner and his colleague Dr. Richard Hift at the University of Cape Town (UCT) were studying VP and its symptoms to better understand how it affects the South African population. Dailey drew the South African's attention with his research on protoporphyrinogen oxidase (PPO), one of the enzymes required to make heme. A defect in PPO is the key element in the onset of porphyria.

Producing heme requires eight different enzymes. When any one of these enzymes malfunctions, porphyrins build up in the blood resulting in porphyria. The human body makes the heme molecules it needs like an assembly line. Enzymes add each piece sequentially to create the finished product. Therefore, anything that affects one part of the assembly line will have an impact on the other part of the assembly line. However, scientists have yet to understand how the overproduction of porphyrins causes the skin sensitivity and abdominal pains.

Since Dailey's group was the first to purify the PPO enzyme, Dr. Meissner arranged to do post-doctoral studies in Georgia, thus creating the foundation for a future partnership. Then he invited Dr. Dailey to South Africa to share laboratory techniques. Two years later, Dr. Meissner, arranged to work on another project in Georgia: identifying the mutation responsible for variegate porphyria. Together, Meissner and Dailey first found the normal PPO gene, or the chain of molecules within DNA that acts as a code to make PPO. They then sequenced the gene (determined the order of the molecules in gene) using the enzyme Dailey's lab had already copied. "We had strong clues about what we were looking for and we had samples from patients," Meissner said. "My Cape Town lab was sequencing DNA from a three year old (though

symptoms do not usually appear until puberty) with two copies of the mutation, which made it perfect for research. We both ran the sequences to compare results."

To determine the mutation, they compared the normal PPO sequence to that of a person with the disease. The researchers specifically compared the function of the normal and mutant PPO enzymes and found that the mutant PPO results in variegate porphyria. In order to even begin this process, the researchers needed cells containing the mutation. Because variegate porphyria is a dominant inherited trait, an individual only needs one copy of the mutant gene to develop the disease.

They discovered two different mutations, one of which connected today's South African population to the marriage of Dutch orphan Arlaantje Adriaanse to fellow Dutchman Gerritt Jansz van Deventer at Cape Town in 1688. One of them carried a single, distinctive gene mutation that now constitutes 90 percent of the variegate porphyria cases in South Africa.

Their research opened the door for the development of neonatal screening and improved testing and treatment for VP.

Change the Attitude Toward Pain

According to a recent publication, suicide rates are higher among Porphyria patients than normal. Perhaps, this is due, in part, to the severe pain some people have during a porphyria attack. Since pain care is a problem with some patients, the following may be important to you.

Pain care is a significant public health's issue that is not formally addressed by our health care system. While Medicare and Medicaid treat pain related to an acute episode or to hospitalization, chronic pain is not covered by public or private health care insurance in general. A 1999 study entitled Chronic Pain in America found that only 1 in 4 of those with pain received adequate treatment. Yet untreated or under-treated pain places high cost on our nation's economy. Pain affects over 75 million individuals every year, 50 million of those suffering from chronic pain. The 2002 American Productivity Audit estimates that pain costs our economy over $78 billion in lost productive work time, accounting for approximately 80 percent of lost time within the work environment.

The Pain Care Policy Act of 2003 provides important federal recognition of pain as a priority public health problem in the United States, and authorizes additional federal resources for pain care research, professional education, public awareness and professional training. In addition, it has provisions to improve access to appropriate diagnosis and treatment for pain in federally financed health care facilities and federally financed managed care programs.

Although most people, who have attacks of the acute porphyrias, suffer with pain that subsides as the attack subsides, others endure chronic pain. Because pain treatment sometimes has a related drug-seeking stigma, it is not unusual for people to receive appropriate pain treatment. Fortunately, pain management has become a medical discipline in the last few years. In fact, the force behind making pain management a medical discipline was Dr. Kathleen Foley, who practices at Memorial Sloan Kettering Cancer Center in New York City. Interestingly, she worked on porphyria pain research for many years. Therefore, as APF members, there are two actions members might take. First, download the new treatment brochure for physicians and ask your doctor to read it and place it in your medical file. Next, ask your congressman to support the Pain Care Policy Act of 2003 - H.R. 1863.

Your help is important to improve the attitude about pain in the eyes of the public and medical community.

Yankeegrl11714@aol.com
See People Magazine 8/4/03 re Lauren
Hi, My name is Lauren. I am 17 years old and I live in Kansas City with my Mom, Dad, and younger sister, Morgan who is 14. I also have a dog named, Chopper. She is a golden retriever, who loves attention!

I am in 11th grade, and my favorite subjects are writing, literature and history but writing is the absolute best! I have a lot of hobbies too, like using the computer and chatting with friends, watching movies (especially those with George Clooney), reading books, writing poetry, playing video games, and listening to music! I love sports too, but I can't play them anymore because of my illness.

When I was 13, I got really sick. It started with SEVERE stomach pain and a few other unpleasant symptoms. The doctors tried for quite a while to figure out what was going on. Finally, they discovered I have Porphyria, which causes acute attacks. I get REALLY sick and in pain. I'm unable to walk, and can't use my left arm. I'm pretty much stuck in bed most of the time, which as you can probably guess isn't much fun!

Because of my illness, I have something called a port-a-cath, a small tube inserted in my chest so that I don't have to get stuck all the time to get medicine. It doesn't hurt, really, and since I need the medicine called Panhematin once a month for five days, I'm happy that I have an easy way for it to go from the outside of me to the inside of me. The medicine helps the disease, so I guess it's worth it! I also have something called a jejunal-gastric (j-g) tube. That's a mouthful, huh? Anyway, I can't eat by mouth like other people do, so I am fed through my j-g tube, which goes into my stomach. Weird, huh?

I think I'm a pretty easy going, friendly person, so I pretty much get along with anyone. However, there are a few things that drive me crazy, such as when a healthy kid comes over to my house and starts complaining about the silliest things, like "Oh, I hate my life, or my soccer coach didn't let me play in the whole game!" or "Oh, I just wanna' die! My hair looks sooooo awful!" I guess what I mean is, I hate when people don't realize how lucky they are and when they don't appreciate how awesome their lives really are. Sometimes I feel like saying, "You know, if you think your life is hard, then you should come and spend a day at my hospital with me and all the other patients there. That would really make you appreciate what you have."

I would love to share this bit of Lauren advice with the whole world: Appreciate life, appreciate your health, and appreciate the people around you who love you. You just don't know what you have 'til it's gone!

Because of my illness, I am home-schooled and have some really nice teachers from the local high school. They come twice a week, and I really enjoy my time with them a lot! I know it sounds kind of nuts, but I actually like homework...It gives me something to do during the day when I feel up to it! I think the best thing about being home-schooled is that I can concentrate really well, because there aren't any distractions, and I can ask questions any time I want because it's just the teacher and me. I think the worst thing about it is I really miss my friends a lot, and it can be pretty lonely being in a class all by myself! It's pretty hard to pass notes when you're home-schooled, because the only person you can pass a note to is yourself!

One last piece of advice...one I think is most important:

Please treat kids with an illness or disability the same way you would anyone else, because inside we are just like everyone else! We may have physical problems and look a little different on the outside, but what

matters is what's inside.

Camp for EPP Kids in California

There's a camp in Northern California, which is interested in hosting a group of EPP kids and their families at a weeklong camp next year. According to their Director, Christine Tenconi, Camp Wonder, which is a part of the Children's Skin Disease Foundation, is free to campers, their siblings and their immediate families. They can accommodate around 25 families and will be able to meet their needs by planning inside activities during the day and several evening activities, including campfires, horseback riding, swimming and a talent show, so that we can have fun when the sun goes down! She described the "camp" as a hotel in the woods, so we'd be in air-conditioned rooms with showers, a dining hall and any additional accommodations that we need, including an on-site medical staff.

They agreed to make us comfortable by putting film on the windows, shades anywhere we need them, providing golf carts to get the kids to and from different places (so that they don't have to walk in the sun) and they're even installing misters in several areas (without my even asking) as other children they service need cool air on their skin as well. We would even have our own time there with EPP families. If we couldn't get enough kids to fill an entire camp, the Director will work with us to find another group of children with similar skin issues to join us.

Please forward this message on to anyone that you know who has EPP, knows someone with EPP or has a newsletter, website or keeps in contact with families of children with EPP. I'm hoping that if enough people are interested, we'll be able to make this dream a reality. If you have kids, are a kid or know a kid who is interested, please email me, and I will put you on our list of campers and keep you informed of our progress for filling up the camp. If you have any additional questions, please feel free to email me at: abdesign@aol.com.

My daughter, Carly (see Summer APF newsletter for an article about her), and my husband have EPP, so I'm totally committed to finding a place where they can enjoy themselves with other people who have the same disease.

Here's their website in case you want to check out the camp: www.csdf.org. Thank you for your help. I look forward to hearing from you.
Sincerely, Kim Moya

The Hunt Goes On

For years, debates about the royal porphyria have raged between medical professionals and historians. As far back as the 1960s, the psychiatrists Macalpine and Hunter claimed that the disease was inextricably linked with the crown of England. They argued that the 'mad' George III had actually been suffering from porphyria, citing the tell-tale symptom of purple urine as proof. It took a unique partnership between John R^hl, a history professor and two British geneticists, to uncover more proof about the royal remains and the Porphyria question. John wrote a letter to The Guardian to support his porphyria argument. The two geneticists, Martin Warren and David Hunt, spotted the letter, and the three then forged a partnership, which saw them hunting down the remains of long-dead royals for a dusting of their DNA. Just a tiny sample of bone marrow could prove their theory conclusively.

John's research pointed towards at least three royals who had almost certainly had porphyria. Queen Victoria's grandchild Charlotte, the sister of Kaiser Wilhelm, wrote of having terrible abdominal pains, being lame, having blisters on her face and of having dark red urine. John found references to similar symptoms

in the correspondence of her mother, who was Queen Victoria's daughter and of her daughter, Feodora.

The three academics sought permission to open Charlotte's grave. When it was first opened, the royal shroud still lay over the coffin. Scraping some bone marrow from her femur, they tested it and found the results positive for the porphyria. The researchers felt that the chances of her having it independently from George III are almost impossible. The Queen's cousin, William of Gloucester, who died in a plane crash in 1972, was clinically diagnosed with the same type of porphyria by three different doctors in three parts of the world, thus, adding to the proof.

Recently, John was given permission to examine the heart of James II in hopes of finding when the disease entered into the family. Also, some historians believe it originated with Mary Queen of Scots. John's book, The Purple Secret, allows the genealogy of the disease to be traced back for hundreds of years and sheds new light on European history. John received an award of over £95000 from the Arts and Humanities Research Board in support of his work on Kaiser Wilhelm II.

What Does the APF Do For You?

This is your organization. We cannot operate without your help. Your donations help fund the many important services listed below:

- Produces award winning brochures and newsletters
- Produces other comprehensive information for patients and physicians on topics from pre-diagnosis to post-treatment
- Fulfills approximately 5000 requests a year
- Maintains and updates the APF website, which is visited by tens of thousands of people annually
- Funds and locates participants for research projects
- Maintains a telephone hot-line
- Acts as intermediary between patients and drug companies
- Retains a Scientific Advisory Board of the world experts
- Oversees a national support network
- Develops public policy and participates in policy issues
- Identifies and promotes rare disease legislation
- Provides a means of interaction among patients
- Establishes support groups around the country
- Maintains a reference center to identify porphyria specialists
- AND MANY MORE

In addition, this past year we have performed the following:

- Opened the APF website for the general public
- Played a major part in the increased government funding for Rare Diseases
- Lobbied against reimbursement cuts in the Rare Disease Medicare legislation
- Produced a comprehensive Diagnosis and Treatment brochure for physicians for November publication
- Supported two major research projects
- Provided patient volunteers for three major research projects
- Featured patient experiences in the APF publications
- Represented the APF on the board of the National Organization of Rare Diseases-NORD
- Represented Porphyria patients at the Coalition of Chronic Pain meetings and publications
- Collaborated with Ovation Pharmaceuticals on heme therapy issues and the initiation of a Scientific

Advisory Panel
- Assisted in the transition issues with Panhematin
- AND MANY MORE

Websites-FYI

The diagnosis and treatment of childhood porphyrias:
http://www.mayo.edu/proceedings/2002/aug/7708sc.pdf

Biochemical diagnosis and monitoring therapeutic modulation of disease activity in an unusual case of congenital erythropoietic porphyria (CEP):
http://www.clinchem.org/cgi/content/abstract/31/12/1946

A mouse model of familial porphyria cutanea tarda:
http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=14578

Special praise for APF-SAB member, Dr. Claus Pierach:
http://www.acponline.org/chapters/mn/newsletters/winter2001.htm

Research Volunteers Needed

Volunteers for the enzyme replacement studies are still needed. The research will take place at the laboratories of Dr. Karl Anderson in Galveston, Texas and Dr. Herbert Bonkovsky in Farmington, Connecticut. The focus of their research is to replace the deficiency of the PBGD enzyme for acute intermittent Porphyria (AIP) and, in turn, relieve or prevent symptoms of the disease.

Volunteers should have a definite diagnosis for AIP and must be experiencing frequent attacks. Remember research is the key to your cure, so if you are interested in participating as a research patient, please contact Desiree at the APF office or email porphyrus@aol.com to Desiree's attention.

Want To Take A Cruise

If you are interest in taking a cruise with other members of the APF, please email Desiree at lyonapf@aol.com or contact her at the office. A few of the potential destinations are: Alaska, the Adriatic or the Mediterranean. The suggested time will be next spring or summer.

The destination of the cruise will depend on the level of response we receive from our members. The cruise lines will be one of the following: Raddison, Silver Sea, Crystal Cruise or Seabourn. Again the selection is dependent on the response we receive from our members. Therefore, if you have a preference of a certain destination or a preference for a specific cruise line, please email your suggestions or contact us at the office. Cruising will provide us with a special opportunity to enjoy fabulous sights, meet other members, learn about porphyria and eat far too much.

If you would like to have time to learn about porphyria, we will set aside time on the "sailing only day" to have special sessions to focus on the diagnosis, tretment and new developments in the area of the porphyrias.

Please express your interest as soon as possible by emailing Desiree or calling the APF office. 713-266-9617.

In Memory

Larry and Beverly Roberts have made a donation in memory of their family members, Elmer Emerick and Kenneth (Bud) Simnitt. We send them our sympathy and thanks for their generosity.

The APF also received a generous donation in memory of John H. Giacobbe, an EPP patient, who passed away Nov. 21, 2002. We extend our sincerest sympathy to his wife and family.

Please notify the APF if you have a family member or friend who has passed away.

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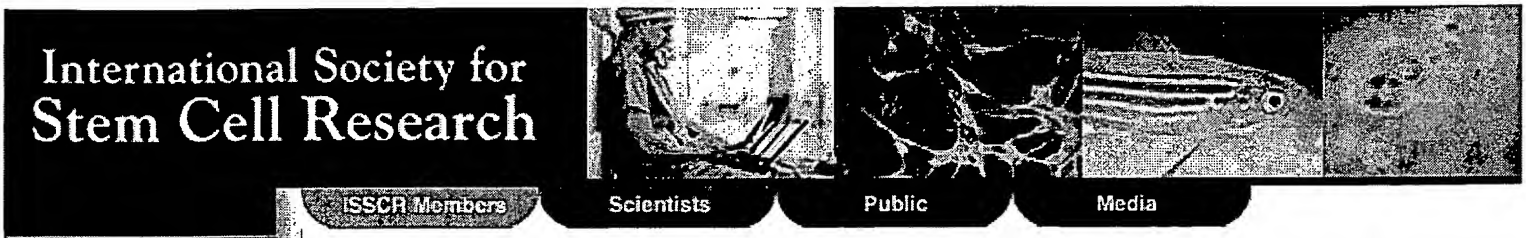

The Basics
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FAQ

The answers to the following questions were written and reviewed by a panel of scientists who specialize in stem cell research. Click on the question to go directly to the answer or scroll through the list to view the entire FAQ.

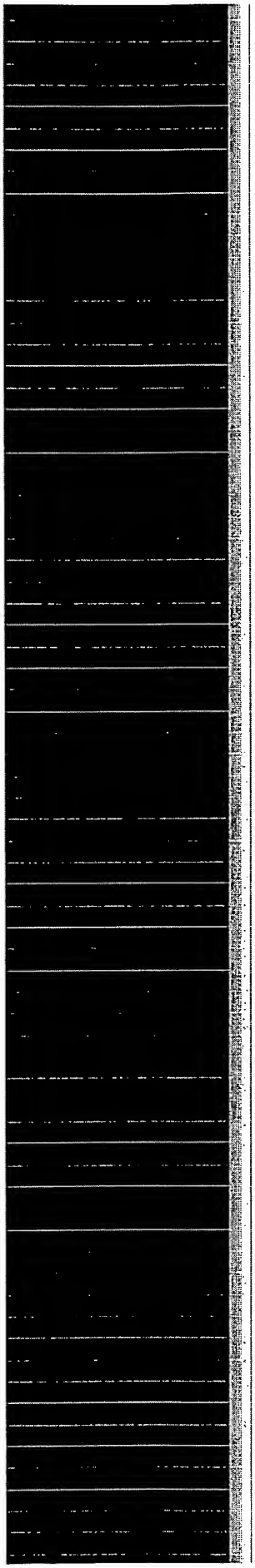
Download a printable version of the ISSCR FAQ (204 KB PDF).

Questions

1. What are stem cells?

Stem cells are the foundation cells for every organ, tissue and cell in the body. They are like a blank microchip that can ultimately be programmed to perform any number of specialized tasks. Stem cells are undifferentiated, "blank" cells that do not yet have a specific function. Under proper conditions, stem cells begin to develop into specialized tissues and organs. Additionally, stem cells are self-sustaining and can replicate themselves for long periods of time.

These unique characteristics make stem cells very promising for supplying cells to treat debilitating diseases like Alzheimer's disease, cancer, Parkinson's disease, type-1 diabetes, spinal cord injury, stroke, burns, heart disease, osteoarthritis and rheumatoid arthritis. Today, donated organs and tissues are often used to replace those that are diseased or destroyed. Unfortunately, the number of people needing transplants far exceeds the number of organs available. Stem cells offer the potential for supplying cells and tissues, which can be used to treat these various diseases.



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2. Where do stem cells come from?

All human beings start their lives from a single cell, called the zygote, which is formed after fertilization. The zygote divides and forms two cells; each of those cells divides again, and so on. Pretty soon, about five days after conception, there is hollow ball of about 150 cells called the blastocyst. The blastocyst is smaller than a grain of sand and contains two types of cells, the trophoblast and the inner cell mass. Embryonic stem cells are the cells that make up the inner cell mass. As embryonic stem cells can form all cell types in an adult, they are referred to as pluripotent stem cells.

Stem cells can also be found in very small numbers in various tissues in the adult body. For example, bone marrow stem cells are found in the marrow of the bone and they give rise to all specialized blood cell types. Adult stem cells are typically programmed to form different cell types of their own tissue; they are called multipotent stem cells. Adult stem cells have not yet been identified in all vital organs. In some tissues like the brain, although stem cells exist, they are not very active, and thus do not readily respond to cell injury or damage. Scientists are now also exploring ways in which they can induce the stem cells already present to grow and make the right cell types to replace the damaged ones.

Stem cells can also be obtained from sources like the umbilical cord of a newborn baby. This is an accessible source of stem cells, compared to adult tissues like the brain and bone marrow. Although scientists can grow these cells in culture dishes, they can do so only for a limited time. Recently, scientists have discovered the existence of stem cells in baby teeth and in amniotic fluid-the "water bath" that surrounds an unborn baby- and these cells may also have the potential to form multiple cell types. Research to characterize and study these cells is very promising but at a very early stage.

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3. What are the potential uses of human stem cells?

Most of the body's specialized cells cannot be replaced by natural processes if they are seriously damaged or diseased. Stem cells can be used to generate healthy and functioning specialized cells, which can then replace diseased or dysfunctional cells.

Replacing diseased cells with healthy cells, called cell therapy, is similar to the process of organ transplantation only the treatment consists of transplanting cells instead of organs. Some conditions or injuries can be treated through transplantation of entire healthy organs, but there is an acute shortage of donors. Stem cells can serve as an alternate and renewable source for specialized cells. Currently, researchers are investigating the use of adult, fetal and embryonic stem cells as a resource for various, specialized cell types, such as nerve cells, muscle cells, blood cells and skin cells, that can be used to treat various diseases.

For example, in Parkinson's disease, stem cells may be used to form a special kind of nerve cell, a kind that secretes dopamine. These nerve cells can theoretically be transplanted into a patient where they will re-wire the brain and restore function, thus treating the patient.

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4. What are the obstacles that must be overcome before the potential uses of stem cells will be realized?

One of the first obstacles that must be overcome is the difficulty in identifying stem cells from adult tissues, which contain numerous mixtures of various cells. The process of identifying and growing the right kind of stem cell, usually a very rare cell in the adult tissue, involves painstaking research.

Second, once stem cells are identified and isolated, the right conditions must be developed to cause these cells to differentiate into the specialized cells. This too will require a great deal of experimentation.

In general, embryonic and fetal stem cells are believed to be more versatile than adult stem cells. However, scientists are still working on developing proper conditions to differentiate embryonic stem cells into specialized cells. As embryonic stem cells grow very fast, scientists must be very careful in fully differentiating them into specialized cells. Otherwise, any remaining embryonic stem cells can grow uncontrolled and form tumors.

Assuming that the above obstacles can be overcome, new issues arise when the specialized cells (grown from stem cells) are implanted into a person. The cells must be integrated into the patient's own tissues and organs and "learn" to function in concert with the body's natural cells. Cardiac cells that beat in a cell culture, for example, may not beat in rhythm with a patient's own heart cells. And neurons injected into a damaged brain must become "wired into" the brain's intricate network of cells and their connections in order to work properly.

Yet another challenge is the phenomenon of tissue rejection. Just as in organ transplants, the body's immune cells will recognize transplanted cells as "foreign," setting off an immune reaction that could cause the transplant to fail and possibly endanger the patient. Cell recipients would have to take drugs to temporarily suppress their immune systems, which in itself could be dangerous.

Thus, research on stem cells and their applications to treat various diseases is still at a preliminary stage. However, results from animal models are very promising and many researchers believe that it is only a matter of time before the same results can be achieved with human stem cells.

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5. What is a stem cell line?

A stem cell line is composed of a population of cells that can replicate themselves for long periods of time in vitro, meaning out of the body. These cell lines are grown in incubators with specialized growth factor-containing media, at a temperature and oxygen/carbon dioxide mixture resembling that found in the mammalian body.

Embryonic stem cell lines, both human and mouse, can be grown indefinitely in vitro if the correct conditions are met. Importantly, these cells continue to retain their ability to form different, specialized cell types once they are removed from the special conditions that keep them in an undifferentiated, or unspecialized, state.

A limited number of human embryonic stem cell lines have been approved for use by scientists receiving federal funds in the United States. In August 2001, President Bush mandated that if scientists were using federal funds, research could only be conducted on the cell lines that were already in existence, grown from fertilized eggs that were to be discarded at in vitro fertilization clinics.

This regulation stated that no additional human stem cell lines could be generated from additional blastocysts. In the long term, this will place severe restrictions on the scientific process in this field and will limit the ability of scientists to compare the potential of human embryonic stem cell lines for tissue repair, to that which can be accomplished from other sources, such as adult stem cells.

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6. What is an embryonic stem cell?

Embryonic stem cells are derived from the cells that make up the inner cell mass of the blastocyst. Both mouse and human embryonic stem cell lines exist. Mouse embryonic stem cells are capable of generating any and all cells in the body, under the right conditions. Therefore, they are said to be pluripotent and have unlimited potential as far as growth and differentiation. The cells divide continuously in tissue culture dishes in an incubator, but at the same time maintain the ability to generate any cell type when placed into the correct environment to cause their differentiation.

Human embryonic stem cell lines are currently being studied and several research teams are working to determine whether or not they possess the same properties as mouse embryonic stem cells. Because

human embryonic stem cells were isolated relatively recently, and therefore we know less about them, it is currently more difficult to work with human systems than mouse. However, scientists are making remarkable progress that could ultimately lead to therapies to replace or restore damaged tissues using these human cells.

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7. What is an adult stem cell?
Adult stem cells are distinct from cells isolated from embryos or fetuses and are found in tissues that have already developed, as in animals or humans after birth. These cells can be isolated from many tissues, including brain. However, the most common place to obtain these cells is from the bone marrow that is located in the center of some bones. The marrow is harvested from human donors at the iliac crest (the back of the upper hip bone).

There are different types of stem cells found in the bone marrow, including hematopoietic stem cells, endothelial stem cells, and mesenchymal stem cells. It has long been known that hematopoietic stem cells form blood, endothelial stem cells form the vascular system (arteries and veins), and mesenchymal stem cells form bone, cartilage, muscle, fat, and fibroblasts.

Recently a theory of "stem cell plasticity" has been put forth, which suggests that some adult stem cells may have a broader potential to form different cell types than was previously suspected. That means cells from the bone marrow, originally thought to be purely blood-forming cells, may contribute to regeneration of damaged livers, kidneys, hearts, lungs and other organs.

Although this field is extremely exciting, it is highly controversial in the scientific community and needs additional carefully documented research to understand the full potential of the adult stem cells, and in particular how they compare to embryonic stem cells.

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8. What is unique about stem cells from baby teeth or umbilical cords?
Stem cells from umbilical cord blood or the pulp under baby teeth are "younger" stem cells than those obtained from adults. They are able to divide for longer times in cell cultures than most adult stem cells, and may give rise to different tissues. Their potential to form many different cell types is currently being explored.

Umbilical cord blood stem cells are used for stem cell transplantation to reconstitute blood cell formation (the hematopoietic system) in patients that have been irradiated or treated with specific drugs for cancer or leukemia. Also, in some genetic diseases, where patients have a problem forming normal blood cells, a transplantation of matched umbilical cord blood cells can give them a new blood-forming system.

The new cells are infused into the vein of the patient and then they are able to find their way into the bone marrow, in a process called "stem cell homing."

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9. Are some kinds of stem cells better than others?
The field of stem cell research involves the study of these cells for many reasons. Some scientists are examining stem cells to better understand the process of development to learn how specific cell types and specific tissues and organs are formed. Some scientists are looking at stem cells to understand what goes wrong in cells to cause various diseases. For these purposes, valuable information can be gained by studying any of the stem cell types that are currently available.

The most publicized use for stem cells, however, is their ability to form different types of cells that can be

used to restore or replace damaged tissue in patients with disease or injury. From studies using mice, it was found that mouse embryonic stem cells could contribute to every tissue in the adult mouse. It is believed that human embryonic stem cells have this property, and are called pluripotent stem cells. Scientists now need to compare human embryonic stem cell lines for their potential in tissue repair to that which can be accomplished from adult stem cells.

Currently, it is not clear whether stem cells from adult tissues or umbilical cord blood are pluripotent. The comparison of human embryonic stem cells to adult stem cells is currently a very active area in research, and one that will hopefully lead to cures for tissue degenerative diseases in the future.

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10. Do stem cells come from aborted fetuses?
One potential source of stem cells comes from early fetal tissue recovered during a narrow window of development. In development, an embryo is called a fetus at about 7-8 weeks following fertilization. At about 4-5 weeks of development, embryonic germ cells, the precursors to the egg and sperm cells, are found in the developing ovary or testis, structures only about 2 mm long.

In 1998, the isolation, culture and partial characterization of embryonic germ cells were reported. The cells were derived from human aborted tissue. When isolated and cultured, these germ cells were shown to have properties similar to stem cells isolated from the inner cell mass of blastocysts.

However, some evidence has suggested that embryonic germ cells may be more limited in their ability to become many different cell types because they are isolated from tissue that is further along in development (several weeks as opposed to only 4-5 days). More research will be required to understand the properties and behavior of these cells to determine their usefulness for future cell therapies. Because of various discrepancies in federal regulations, stem cells taken from fetuses are subject to different rules that stem cells derived from embryos.

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11. What diseases can be cured by using stem cells?
The most promising use of stem cells is due to their ability to be modified into different functional adult cell types and serve as a potential source of replacement cells to treat numerous diseases. Thus, any disease in which there is tissue degeneration can be a potential candidate for stem cell therapies, including conditions and disabilities as Parkinson's and Alzheimer's diseases, spinal cord injury, stroke, burns, heart disease, Type 1 diabetes, osteoarthritis, rheumatoid arthritis, muscular dystrophies and liver diseases.

In addition, retinal regeneration with stem cells isolated from the eyes can lead to a possible cure for damaged or diseased eyes and may one day help reverse blindness. Hair stem cells have also been isolated and could help people with hair loss by allowing hair cell regeneration.

Embryonic stem cells, which can form all types of functional adult cells, provide the hope that one day such cells can produce the cells or tissues to grow entire hearts, liver and even kidneys, thus solving the problem of the shortfall of organ donors.

Adult stem cell replacement, through bone marrow transplantation with a matched donor, has been a well-established treatment for blood cancers and other blood disorders. However, significant toxicity and donor availability limit this approach to a minority of affected individuals. It is hoped that genetic alteration a patient's own bone marrow stem cells, and subsequent transplantation, will provide a viable alternative; however, these techniques for genetic manipulation must be improved before this is ready for clinical application.

Recently, new possibilities for the use of adult stem cells have emerged when researchers showed that cells from the bone marrow can give rise to specialized cells in a variety of tissues as different as blood, brain, muscle, kidney, pancreas and liver. One can imagine that one day, we will be able to isolate our own bone marrow cells, treat them and reintroduce them back into the body to renew or repair cells in a number of

different organs.

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12. Are stem cells currently used in therapies today?
Hematopoietic stem cells (HSCs), present in the bone marrow and precursors to all blood cells, are currently the only type of stem cells commonly used for therapy. Doctors have been transferring HSCs in bone marrow transplants for more than 40 years. Advanced techniques for collecting or "harvesting" HSCs are now used to treat leukemia, lymphoma and several inherited blood disorders.

The clinical potential of stem cells has also been demonstrated in the treatment of other human diseases, including diabetes and advanced kidney cancer. However, these new therapies have been offered only to a very limited number of patients using adult stem cells.

New clinical applications for stem cells are currently being tested therapeutically for the treatment of liver diseases, coronary diseases, autoimmune and metabolic disorders (amyloidosis), chronic inflammatory diseases (lupus) and other advanced cancers.

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13. What is the difference between therapeutic cloning and reproductive cloning?
Reproductive cloning is the process by which an embryo is created by nuclear transfer and implanted into a surrogate mother in the hope of bringing it to term. Therapeutic cloning is the process by which an embryo is created through nuclear transfer in order to obtain stem cells from it for therapeutic purposes.

Reproductive cloning means creating a new individual from a single cell by replacing the nucleus in an egg cell with the nucleus (containing the genetic material) from another cell of the body. The cloned egg cell grows and develops into an embryo. The embryo is implanted inside a surrogate mother's womb to mature and produce a viable fetus. After birth the clone would, in theory, be the genetic copy of the adult whose nucleus was used for cloning. Reproductive cloning performed in animals is burdened by many technical and biological problems. Only about 1percent of all the eggs that receive donor DNA can develop into normal surviving clones. In addition, the clones that survive often present many health problems.

Therapeutic cloning uses cloning technology to develop stem cells for research, and ultimately for therapy. The nucleus of the egg cell is replaced with the nucleus of another cell from the body and the egg cell is allowed to grow for about 4-5 days and develop to the blastocyst stage. The inner cell mass of the blastocyst is then removed and used for the creation of an embryonic stem cell line that has the genetic makeup of the donated nucleus. The goal of therapeutic cloning is to produce human stem cells, and subsequent tissues and organs, which can be used to replace damaged tissue. It is an application of the cloning technology which does not result in the production of genetically identical fetuses. One of the major problems facing the widespread use of this stem cell therapy is the fact that the transplanted cells, or tissues, are likely to be rejected by the patient's immune system. Therapeutic cloning would allow the production of cells and tissues matching each individual patient because the donated nucleus would come from the patient. Thus, the cells would genetically match the patient and would not elicit rejection when they are transplanted into the patient.

There continue to be great differences in the way countries around the world regulate human cloning and related technologies. For instance, it appears to be well accepted that a distinction must be made between the application of cloning techniques to the replication of a person, and the application of cloning techniques to the creation of tissues and cell lines with the aim of developing therapies. The use of cloning techniques for reproductive purposes has brought international condemnation and there appears to be a consensus against reproductive cloning.

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14. Why is stem cell research confused with cloning?
Stem cell research is often confused with cloning because both areas involve the use of embryonic cells. The public and the media often equate "cloning" with the manipulation of embryonic cells to produce an organism, and stem cell research was first brought to the spot light when human stem cells were isolated from human "embryonic tissues". Both fields got even more confused when the term therapeutic cloning was introduced as a means to produce embryonic stem cells. But stem cell research does not always involve embryonic stem cells.

While reproductive cloning (the production of a whole new individual from one original cell by cloning technology) and therapeutic cloning (the use of cloning for the isolation of stem cells) both use techniques involving embryos, stem cell research involves the use of several different types of cells besides embryonic stem cells, such as adult stem cells from humans or animals, or stem cells from fetuses, umbilical cord or amniotic fluid.

Thus, a clear line should be drawn between cloning for the production of a cell or organism with the same nuclear genome as another cell or organism and stem cell research, which is based on the isolation of adult and embryonic stem cells in order to find cures for many degenerative diseases.

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15. What is somatic cell nuclear transfer?
Somatic cell nuclear transfer, also called SCNT, is a technique in which the nucleus of a somatic cell (any cell of the body except sperm cells and egg cells) is injected, or transplanted, into an egg, that has had its nucleus removed. If the new egg is then implanted into the womb of an animal, an individual will be born that is a clone. The clone has the identical genetic material as the somatic cell that was transplanted because the nucleus that carries the genetic material.

This procedure is very inefficient and was first developed for agricultural purposes. However, in human medicine, this technique can be used to isolate embryonic stem cells from eggs that undergo nuclear transplantation. When the somatic cell is supplied from the cells of a person, the stem cells isolated from the developing eggs can be used to make a tissue that will not be rejected by that person, because they have the same genetic material. In this way, 'customized' embryonic stem cells could be made for everyone who needed them.

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16. How are stem cells grown in the laboratory?
Stem cells are generally grown in culture dishes in incubators at body temperature (37°C) under high humidity. Because there are many different types of stem cells, the components of the culture solutions for each type of stem cell, are different. The challenge for scientists is to grow enough stem cells in an undifferentiated state, that is without having them differentiate into more specialized cell types, and also to learn how to make the cells differentiate into specialized cells, when that becomes necessary.

Human embryonic stem cells can be grown as small colonies on layers of skin cells in the presence of serum from the blood. The skin cells are known as "feeder cells" and together with the serum, provide unknown factors that nourish and support the embryonic stem cells in their undifferentiated state. When the colonies of embryonic stem cells grow too big for their culture dishes, they are divided into smaller colonies, or single cells, and transferred into new culture dishes. The cells then continue to grow. This transfer process, known as "passaging", can theoretically be repeated indefinitely.

Hematopoietic stem cells can be derived from either bone marrow, placenta or umbilical cord blood. It is currently very difficult to grow hematopoietic stem cells in culture, as they tend to differentiate into more advanced cell types very quickly. Therefore, hematopoietic stem cells are not generally grown in culture.

Human mesenchymal stem cells, or bone marrow stromal stem cells, are isolated from the bone marrow and grown in culture media supplemented with serum from the blood. Mesenchymal stem cells attach to the plastic on the bottom of the culture dishes and can grow for several weeks before they will differentiate into

other cell types.

Human neural stem cells can grow from fetal or adult brain tissue in culture media. They grow in suspension, meaning they do not attach to a culture dish, and they do not need serum from blood. In culture, one single neural stem cell can divide to make more cells that together form a round hollow structure known as a neurosphere. Neurospheres continue to grow in culture and when they get too big, are disaggregated into single cells.

These single cells are a mixed population of neural stem cells and more mature cells. The neural stem cells can be selected from this mixed population and once again grown into round and hollow neurospheres. This process of disaggregation and neurosphere formation can be repeated several times. Eventually all the neural stem cells differentiate into more mature cells.

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17. What kinds of experiments have been done with stem cells and what still needs to be done?
Mouse embryonic stem cells were first described in 1981. The most common types of experiments performed have been to genetically manipulate the DNA within the mouse embryonic stem cells. These experiments have provided a large amount of information on the role that different genes play during mouse development, the formation of different tissues and their role in the adult mouse.

Further, it has been known for years that under the right conditions, mouse embryonic stem cells can contribute to every tissue in the body of the mouse. Experiments that uncovered this phenomenon were conducted by putting mouse embryonic stem cells into a fertilized mouse egg at the blastocyst stage, and examining the mouse that is subsequently generated.

These types of experiments cannot be done with human tissues, thus the potential for human embryonic stem cells must be studied in different ways. The human embryonic stem cells can be studied in vitro (in cell culture conditions) or in special mice that are immune deficient, meaning they will not reject cells from a different species.

Human embryonic stem cells were first described in 1998. The lessons learned from working with mouse embryonic stem cells are rapidly being transferred to human embryonic stem cell systems. Scientists are working hard to understand the properties of these cells and to understand the mechanisms that regulate their differentiation into adult cell types. In addition, many researchers are using these cells to set up models to study early human development and also to provide genetic and cell-based therapies for disease.

To this end, it is hoped to better understand the causes of fetal malformations so they can be treated. It is also hoped that one day we will be able to produce cells in dishes, such as heart, pancreas or brain cells, to replace genetically faulty tissue or tissue damaged as a result of heart attacks, diabetes, spinal cord disorders and Parkinson's disease.

Cell transplantation experiments using mouse models for each of these disorders have been conducted with mouse embryonic stem cells and, in some cases, with human embryonic stem cells. Although it is still in its early days, promising results are emerging.

Hematopoietic stem cells are routinely transplanted following irradiation therapies to treat patients with cancer. Irradiation can destroy the cancer cells, but it also destroys the body's hematopoietic stem cells of the bone marrow leaving the patient without an effective immune system.

In these cases, after irradiation therapy is complete, donor hematopoietic stem cells are transplanted back to the bone marrow to restore the patient's immune system. Experiments involving the transplantation of hematopoietic stem cells to sick fetuses during pregnancy have also been undertaken. These fetuses are generally detected to have genetic defects of their own hematopoietic stem cells. These experiments have been met with some success for the treatment of babies who would have otherwise suffered a range of immunodeficiency disorders, thalassemias and inborn errors of metabolism.

Fetal neural stem cell derivatives have been transplanted to replace damaged cells in experiments aimed at controlling the symptoms of Parkinson's disease. These experiments have been similarly met with some success. Experiments injecting stem cells found in mouse blood vessel walls back into the blood vessels of

muscles have been successful in replacing muscle fibers and returning movement to mice with muscle disorders. Mesenchymal stem cells have proven effective in treating mice with genetic liver disease.

Some of the primary experiments that still remain to be performed include those aimed at understanding the factors required to make embryonic stem cells differentiate into the desired cell types; those to understand how to increase the number of stem cells that are accepted by the patient at the correct location in the body during disease; those to reduce host resistance to the new stem cells; and those experiments to ensure that the new stem cells correctly integrate in the body to restore the proper function to the damaged tissue.

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18. Can cord blood or stem cells be stored in a bank?
Human cord blood, neural stem cells and human embryonic stem cell banks have been established in various countries and are currently being expanded. Cord blood, like bone marrow, is stored as a source of hematopoietic stem cells for the treatment of specific genetic and acquired diseases in allogeneic stem-cell transplantation therapies.

Neural stem cells, which are derived from aborted fetuses, are stored in banks for the potential treatment of brain specific diseases. Embryonic stem cell banks have also been established for the potential treatment of a wide variety of genetic and acquired diseases, ranging from neural to blood to pancreatic to heart to skin.

Prior to banking, quality control procedures check for: chromosomal abnormalities, the ability of the stem cells to undergo the freeze-thawing processes, the immune compatibility of the stem cells with patients potentially requiring the cells, the presence of viruses within the stem cells that may cause disease, the ability of the stem cells to give rise to the required adult cell types when required, and the ability of the stem cell numbers to be increased to useful amounts.

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19. What is regenerative medicine?
The goal of regenerative medicine is to repair organs or tissues that are damaged by disease, aging or trauma, so that function can be restored, or at least improved. Using this definition, most medical acts can be considered "regenerative," except those that are aimed at prevention of disease such as vaccination.

The term regenerative medicine is used nowadays to describe medical acts, treatments and research that use stem cells (either adult or embryonic) to restore the function of organs or tissues. This can be achieved in different ways; first, by administering stem cells, or specific cells that are derived from stem cells in the laboratory; or second, by administering drugs that coax stem cells that are already present in tissues to more efficiently repair the involved tissue.

Currently, the only routinely applied medical practice using stem cells is for bone marrow transplantation. The use of human embryonic stem cells for therapy is still in its developing stages, but is showing promising experimental results.

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20. How many human embryonic stem cell lines are there?
The available number of human embryonic stem cell lines is a matter of some debate. To date, over 100 human embryonic stem cell lines have been derived worldwide. However, most of those lines are not adequately characterized yet. And only 22 cell lines are eligible for federal funding in the USA. Detailed information on those 22 cell lines can be found at the National Institutes of Health Human Stem Cell Registry at http://stemcells.nih.gov. Information on several of the other cell lines can be found at http://www.isscr.org/science/sclines.htm.
- updated 09.17.04

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21. Why is U.S. federal funding important for stem cell research?
Federal funding for research involving mouse embryonic stem cells and adult stem cells (both mouse and human) is currently available and is not restricted. However, federal funding for research involving human embryonic stem cells is limited to research involving only those cell lines that were approved by the Bush administration in August 2001. In contrast, no restrictions in the type of research that can be performed with private funds are in place. There are several reasons why these limitations are problematic.

In the United States, the National Institutes of Health (NIH) provides the greatest amount of federal funding to scientists on a competitive basis, and holds a long-term perspective on biomedical research, where profit is irrelevant and the progress of science for the benefit of public health is critical. The limited amount of funding from private sources will be unable to keep pace with the needs of the stem cell research community. Less restricted availability of federal funds for human embryonic stem cell research would certainly accelerate progress in this field, and improve the health of the American people in the long-term.

As the regulations now stand, any scientist receiving federal funds is precluded from generating additional human embryonic stem cell lines. It is still not clear to what extent the data obtained with the limited set of cell lines now available, can be generalized to the whole human population, especially given the known variability among different mouse embryonic stem cell lines. In addition, the development of efficient ways to generate new cell lines will likely be necessary if embryonic stem cells are ever to be used for therapies.

Although the private sector can conduct research to generate new cell lines, this can lead to several problems. One is that, because of intellectual property issues, the dissemination of knowledge may be slower when the most cutting edge research is done in private companies. The results of any research performed with private funds would be out of public control, and when knowledge is not in the public domain, progress can be slowed.

A second problem is that private companies need to benefit from their investments and at some point, make a profit. Historically, if profit is deemed unlikely, research can be stopped no matter how important it may be for public health or for the progress of science.

It should be pointed out that research on human embryonic stem cells may not only lead to novel therapies for diseases that are currently difficult or impossible to treat, but also to novel insights into human development and into the nature of our species that could never be obtained from work with experimental animals. This type of fundamental scientific inquiry has generally been funded through the extensive federal government grants program.

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22. What is bioethics?
Bioethics, or medical ethics, is the study of the moral and ethical issues in the fields of scientific research, medical treatment or, more generally, in the life sciences. With advancing technology and modern innovations, new and exciting insights are being gained for many scientific processes and diseases, but at the same time, new questions of medical ethics continually arise.

In the context of reproductive medicine, the ethical issues focus on the rights of individuals to control their bodies or to control the use embryos that are created from their cells. The use of human embryos to isolate stem cells for research and future cell therapy techniques has fueled ethical and public policy debates about the moral status of human embryos and their appropriate use.

Transplantation or research conducted with tissues or organs from aborted fetuses has led to disputes regarding the acceptability of using such tissue.

Cloning animals to produce genetically identical offspring, such as Dolly the sheep, has led many to consider that human cloning may follow and subsequently, has spurred debates about the ethics of creating human clones with the possibility of manipulating specific traits in offspring.

The ethical issues in these areas of research and medicine are still being debated and remain unresolved. They will continue to challenge the scientific, medical and bioethics communities for many years.

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23. Where can I get more information on stem cells?

The Internet provides an excellent source of information on stem cells as well as the current research and clinical studies that are being undertaken. Below is a partial list of some valuable sites:

- The ISSCR Web site, http://www.isscr.org, has valuable information and publishes a newsletter with important information for scientists working in the field.
- The National Institutes of Health Web site has information on stem cells for the public, for scientists and on federal policies.
- Internationally, the Stem Cell Network in Canada also provides some excellent information.
- Stem Cell Research News provides information including an excellent list of stem cell related news articles.
- The Coalition for the Advancement of Medical Research (CAMR) Web site has information on advocacy in the areas of stem cell research and therapeutic cloning.
- A Web site that provides the clinical studies being conducted in the stem cell area can be found at http://www.clinicaltrials.gov.
- Also see the ISSCR Sites of Interest page for a comprehensive listing of stem cell related Web sites.

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24. What other information resources are available?

Try these resources for answers to your questions:

- ISSCR Glossary
- NIH Backgrounder on Stem Cells
- Stem Cell Basics
- Embryonic Stem Cell Basics from the University of Wisconsin-Madison
- Center for Genetics and Society Stem Cell Glossary
- NIH Stem Cell Information

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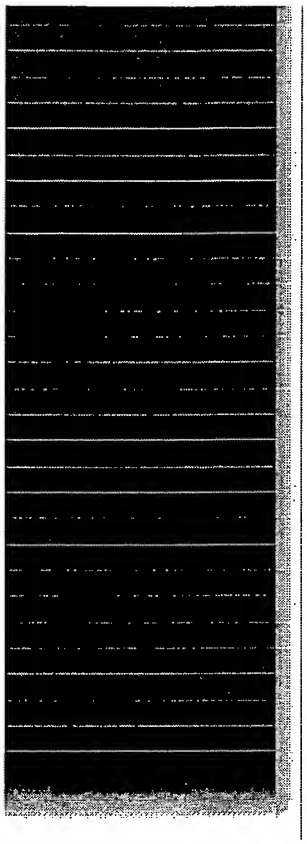
25. Is there an age limit to egg donation for stem cell research?

Human egg donation for stem cell research is an entirely new practice still in the pioneering stages. While appearing frequently in the press, nuclear transfer to derive stem cells (formerly called therapeutic cloning) is still uncharted research frontier territory and not much is known yet.

In humans, a woman's life supply of eggs is present from birth, and during the woman's lifetime mutations accumulate in the DNA of the eggs. Thus, over time, the quality of the eggs declines and risks of genetic defects and developmental abnormalities in fetuses increase significantly. Natural pregnancies in women over 35-40 years old are therefore considered risky. For fertility treatments there is a similar time limit. After the age of 40, egg quality and yield in IVF treatments decline.

However, because eggs donated for stem cell research are enucleated (that is, their DNA is removed) and donor DNA is introduced before stem cells are derived, the age of the egg should not matter. The egg can be simply seen as an incubator for the donor DNA to produce stem cells similar to the DNA donor. However,



there is some indication that eggs from older women have problems with some of the molecules in the cytoplasm of the cells (the part of cells between the outer membrane and the nucleus) that are critical for fertilization and early development. This may affect development of the egg to the blastocyst stage and thus affect derivation of stem cells. As there are not many studies on this yet, it is not known at this point if the age of the egg matters or not.

Nonetheless, unlike blood donation, egg donation is a far more involved and invasive process, including very strong hormone treatments to induce super ovulation. The procedure is similar to that which a woman undergoes for IVF treatment, short of fertilization and implantation of the eggs.

Moreover, human egg freezing is still very experimental and it is not known how well eggs can be frozen and then thawed, without loosing their quality for derivation of stem cells. For example, in fertility treatments, the freezing of unfertilized eggs reduces the later embryo yield. The reasons for this are currently unknown and may not affect stem cell derivation at all. But, potential egg donation would need to take place in a setting located close to a research laboratory equipped for nuclear transfer, in order to immediately start the process of stem cell derivation on fresh eggs.

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Glossary of Stem Cell-Related Terms

The following is a glossary of some stem cell-related terms provided for your convenience. Click a specific word in the list below or scroll through the alphabetized entries.

If a word is missing, contact Suzanne Kadereit at skadereit@enders.tch.harvard.edu to have it added to the list.

Also see the Stem Cell FAQ for answers to frequently asked questions on stem cell research.

See a printable version of the ISSCR Glossary.

Adult stem cells
Stem cells found in different tissues of the developed, adult organism that remain in an undifferentiated, or unspecialized, state. These stem cells can give rise to specialized cell types of the tissue from which they came, i.e., a heart stem cell can give rise to a functional heart muscle cell, but it is still unclear whether they can give rise to all different cell types of the body.

Allogeneic transplantation
Cell, tissue or organ transplants from one member of a species to a genetically different member of the same species.

Autologous transplantation
Cell, tissue or organ transplants from one individual back to the same individual. Such transplants do not induce an immune response and are not rejected.

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Blastocyst
A very early embryo consisting of approximately 150 cells. The blastocyst is a spherical cell mass produced by cleavage of the zygote (fertilized egg). It contains a fluid-filled cavity, a cluster of cells called the inner cell mass (from which embryonic stem cells are derived) and an outer layer of cells called the trophoblast (that forms the placenta).

Bone marrow stromal cell
Also known as mesenchymal stem cells, bone marrow stromal cells are a mixed population of cells derived from the non-blood forming fraction of bone marrow. Bone marrow stromal cells are capable of growth and differentiation into a number of different cell types including bone, cartilage and fat.

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Cell line
Cells that can be maintained and grown in culture and display an immortal or indefinite life span.

Cell type
A specific subset of cells within the body, defined by their appearance, location and function.

i) adipocyte: the functional cell type of fat, or adipose tissue, that is found throughout the body, particularly under the skin. Adipocytes store and synthesize fat for energy, thermal regulation and cushioning against mechanical shock
ii) cardiomyocytes: the functional muscle cell type of the heart that allows it to beat continuously and rhythmically
iii) chondrocyte: the functional cell type that makes cartilage for joints, ear canals, trachea, epiglottis, larynx, the discs between vertebrae and the ends of ribs
iv) fibroblast: a connective or support cell found within most tissues of the body. Fibroblasts provide an instructive support scaffold to help the functional cell types of a specific organ perform correctly.
v) hepatocyte: the functional cell type of the liver that makes enzymes for detoxifying metabolic waste, destroying red blood cells and reclaiming their constituents, and the synthesis of proteins for the blood plasma
vi) hematopoietic cell: the functional cell type that makes blood. Hematopoietic cells are found within the bone marrow of adults. In the fetus, hematopoietic cells are found within the liver, spleen, bone marrow and support tissues surrounding the fe tus in the womb.
vii) myocyte: the functional cell type of muscles
viii) neuron: the functional cell type of the brain that is specialized in conducting impulses
ix) osteoblast: the functional cell type responsible for making bone
x) islet cell: the functional cell of the pancreas that is responsible for secreting insulin, glucogon, gastrin and somatostatin. Together, these molecules regulate a number of processes including carbohydrate and fat metabolism, blood glucose levels and acid secretions into the stomach.

Cloning
The process in which an organism produces one or more genetically alike copies of itself by asexual means. Cloning may occur by propagation of cuttings, as in the case of plants; continual budding, as in the case of hydra; fission, as in the case of bacteria and protozoa; parthenogenic asexual reproduction as in the case of aphids; or somatic cell nuclear transfer, as in the case of higher order animals such as mammals. The term cloning can also be applied to a group of cells undergoing replication by repetitive mitoses (cell divisions).

Also see entries for Reproductive cloning *and* Therapeutic cloning *below.*

Cytoplasm
The part of the cell not including the nucleus.

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Differentiation
The process of development with an increase in the level of organization or complexity of a cell or tissue, accompanied with a more specialized function.

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Ectoderm
The outer of three germ layers of the early embryo that gives rise in later development to the skin, cells of the amnion and chorion, nervous system, enamel of the teeth, lens of the eye and neural crest.

Embryo
The product of a fertilized egg, from the zygote until the fetal stage.

Embryoid bodies
Spheroid colonies seen in culture produced by the growth of embryonic stem cells in suspension. Embryoid bodies are of mixed cell types, and the distribution and timing of the appearance of specific cell types corresponds to that observed within the embryo.

Embryonic germline cells
Embryonic germline cells, also called EG cells, are pluripotent stem cells derived from the primitive germline cells (those cells that give rise to eggs and sperm). Their properties are similar to those of embryonic stem cells.

Embryonic stem cell
Also called ES cells, embryonic stem cells are cells derived from the inner cell mass of developing blastocysts. An ES cell is self-renewing (can replicate itself), pluripotent (can form all cell types found in the body) and theoretically is immortal.

Endoderm
The inner of three germ layers of the early embryo that gives rise in later development to tissues such as the lungs, the intestine, the liver and the pancreas.

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Fetus
The stage in development from the end of the embryonic stage, 7-8 weeks after fertilization, to developed organism that ends at birth.

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Germ layers
The three germ layers are the endoderm, mesoderm and ectoderm and are the three precursory tissue layers of the early, primitive embryo (which form at approximately two weeks in the human) that give rise to all tissues of the body.

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Hematopoietic stem cells
The precursors of mature blood cells that are defined by their ability to replace the bone marrow system following its obliteration (for example, by g-irradiation) and can continue to produce mature blood cells.

Hematopoietic cell transplantation
The transplantation of hematopoietic stem cells with blood-forming potential. Hematopoietic stem cells provide rapid and sustained reconstitution of blood formation and are found in adult bone marrow, umbilical cord blood, peripheral blood and in fetal liver.

Heterologous
Not homologous or uniform. In the context of cells, heterologous is a mixed or divergent cell population or of a divergent origin.

Histocompatible
A tissue or organ from a donor (the person giving the organ or tissue) that will not be rejected by the recipient (the patient in whom the tissue or organ is transplanted). Rejection is caused because the immune system of the recipient sees the transplanted organ or tissue as foreign and tries to destroy it. Tissues from most people are not histocompatible with other people. In siblings, the probability of histocompatibility is higher, while identical twins are almost always histocompatible.

Homologous
Similar or uniform, often used in the context of genes and DNA sequences. In the context of stem cells, the term homologous recombination is a technique used to disable a gene in embryonic stem cells.

Homologous recombination
A technique used to inactivate a gene and determine its function in a living animal. The process of homologous recombination is more efficient in embryonic stem cells than in other cell types. It is achieved by introducing a stretch of DNA that is similar or identical (homologous) to part of a gene and to some of the DNA surrounding the gene, but different (not homologous) to a specific section of the gene. The DNA is then introduced into the stem cells and the stretch of homologous DNA will recognize the similar sequences of the gene within the cell, and replace it. But the cell is then left with a piece of DNA in the gene that has the wrong sequence and this interrupts the function of the gene. The gene is then said to be knocked out. From these embryonic stem cells, an entire mouse can be made by injecting the altered stem cells into a blastocyst, and implanting the blastocyst into a female mouse. This is one way to make genetically manipulated mice and other animals with altered gene function. These experiments are crucial to understand how specific genes work and interact in living animals.

Human embryonic stem cell
A stem cell that is derived from the inner cell mass of a blastocyst and can differentiate into several tissue types in a dish. They are similar to embryonic stem cells from the mouse; however, in the mouse, it is possible to inject those cells into a blastocyst, to make a new mouse, while this is not, and should not, be possible in humans for ethical reasons. Human embryonic stem cells are harder to grow than mouse embryonic stem cells.

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Inner cell mass
A small group of cells attached to the wall of the blastocyst (the embryo at a very early stage of development that looks like a hollow ball). Embryonic stem cells are made by isolating and culturing the cells that make up the inner cell mass. In development. it is the inner cell mass that will eventually give rise to all the organs and tissues of the future embryo and fetus, but do not give rise to the extra-embryonic tissues, such as the placenta.

In vitro fertilization
A procedure where an egg cell (the oocyte) and sperm cells are brought together in a dish (i.e. in vitro), so that a sperm cell can fertilize the egg. The resulting fertilized egg, called a zygote, will start dividing and after a several divisions, forms the embryo that can be implanted into the womb of a woman and give rise to pregnancy.

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Mesemchymal stem cell
Also known as bone marrow stromal cells, mesenchymal stem cells are rare cells, mainly found in the bone marrow, that can give rise to a large number of tissue types such as bone, cartilage (the lining of joints), fat tissue, and connective tissue (tissue that is in between organs and structures in the body).

Mesoderm
The middle of three germ layers that gives rise later in development to such tissues as muscle, bone, and blood.

Morphology
Study of the shape and visual appearance of cells, tissues and organs.

Multipotent stem cells
Stem cells whose progeny are of multiple differentiated cell types, but all within a particular tissue, organ, or physiological system. For example, blood-forming (hematopoietic) stem cells are single multipotent cells that can produce all cell types that are normal components of the blood.

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Neural stem cell
A type of stem cell that resides in the brain, which can make new nerve cells (called neurons) and other cells that support nerve cells (called glia). In the adult, neural stem cells can be found in very specific and very small areas of the brain where replacement of nerve cells is seen.

Nucleus
A part of the cell, situated more or less in the middle of the cell, that is surrounded by a specialized membrane and contains the DNA of the cell. This DNA is packaged into structures called chromosomes, which is the genetic, inherited material of cells.

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Oligopotent progenitor cells
Progenitor cells that can produce more than one type of mature cell. An example is the myeloid progenitor cell which can give rise to mature blood cells, including blood granulocytes, monocytes, red blood cells, platelets, basophiles, eosinophiles and dendritic cells, but not T lymphocytes, B lymphocytes, or natural killer cells.

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Parthenogenesis
A form of reproduction where an egg develops without the fusion of sperm with the egg cell. Parthenogenesis occurs commonly among insects and other arthropods. Artificially inducing parthenogenesis with human eggs may be a means to isolate stem cells from an embryo, without fertilization.

Plasticity
A phenomenon used to describe a cell that is capable of becoming a specialized cell type of different tissue. For example, when the same stem cell can make both new blood cells and new muscle cells.

Phenotype
The description of the characteristics of a cell, a tissue or an animal; as black and white fur of a mouse are two phenotypes that can be found. The phenotype is determined by the genes (or the genotype) and by the environment. For example, short stature is a phenotype that can be genetically determined (and therefore inherited from the parents), but can also be caused by malnourishment during childhood (and therefore be caused by the environment).

Pluripotent stem cells
Stem cells that can become all the cell types that are found in an implanted embryo, fetus, or developed organism, but not embryonic components of the trophoblast and placenta (these are usually called extra-embryonic).

Post-implantation embryo
Implanted embryos in the early stages of development until the establishment of the body plan of a developed organism with identifiable tissues and organs.

Pre-implantation embryos
Fertilized eggs (zygotes) and all of the developmental stages up to, but not beyond, the blastocyst stage.

Progenitor cell
A progenitor cell, often confused with stem cell, is an early descendant of a stem cell that can only differentiate, but it cannot renew itself anymore. In contrast, a stem cell can renew itself (make more stem cells by cell division) or it can differentiate (divide and with each cell division evolve more and more into different types of cells). A progenitor cell is often more limited in the kinds of cells it can become than a stem cell. In scientific terms, it is said that progenitor cells are more differentiated than stem cells.

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Regenerative medicine
Medical interventions that aim to repair damaged organs, most often by using stem cells to replace cells and tissues damaged by aging and by disease.

Reproductive cloning
Somatic cell nuclear transfer used for the production of a fetus and delivery of a live offspring that is genetically identical the donor of the somatic cell DNA.

Also see entries for Cloning *and* Therapeutic cloning.

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Somatic cells
All the cells within the developing or developed organism with the exception of germline (egg and sperm) cells.

Somatic cell nuclear transfer
A technique in which the nucleus of a somatic cell (any cell of the body except sperm cells and egg cells) is injected, or transfered, into an egg, that has had its nucleus removed. If the new egg is then implanted into the womb of an animal, an individual will be born that is a clone. The clone has the identical genetic material as the somatic cell, which supplied the nucleus that carries the genetic material. This procedure is very inefficient and was first developed for agricultural purposes. However, in human medicine, this technique can be used to isolate embryonic stem cells from eggs that have undergone nuclear transfer. When the somatic cell is supplied from the cells of a person, the stem cells isolated from the developing eggs can be used to make a tissue that will not be rejected by that person, because they have the same genetic material. In this way, 'customized' embryonic stem cells could be made for everyone who needed them.

Stem cells
Cells that have both the capacity to self-renew (make more stem cells by cell division) as well as to differentiate into mature, specialized cells.

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Therapeutic cloning
Somatic cell nuclear transfer for the isolation of embryonic stem cells. The embryonic stem cells are derived from the blastocyst (before it becomes a fetus) and can be instructed to form particular cell types (e.g. heart muscle) to be implanted into damaged tissue (e.g. heart) to restore its function. If the stem cells are placed back into the individual who gave the DNA for the somatic cell nuclear transfer, the embryonic stem cells and their derivatives are genetically identical and thus immunocompatible (they will not be rejected).

Also see entries for Cloning *and* Reproductive cloning.

Totipotent stem cells
Stem cells that can give rise to all cell types that are found in an embryo, fetus, or developed organism, including the embryonic components of the trophoblast and placenta required to support development and birth. The zygote and the cells at the very early stages following fertilization (i.e., the 2-cell stage) are considered totipotent.

Transdifferentiation
The ability of a particular cell of one tissue, organ or system, including stem or progenitor cells, to differentiate into a cell type characteristic of another tissue, organ, or system; e.g., blood stem cells changing to liver cells.

Transplantation biology
The science that studies the transplantation of organs and cells. Transplantation biologists investigate scientific questions to understand why foreign tissues and organs are rejected, the way transplanted organs function in the recipient, how this function can be maintained or improved, and how the organ to be transplanted should be handled to obtain optimal results.

Trophoblast
The tissue of the developing embryo responsible for implantation and formation of the placenta. In contrast to embryonic stem cells, the trophoblast does not come from the inner cell mass, but from cells surrounding it.

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Umbilical cord stem cells
Hematopoietic stem cells are present in the blood of the umbilical cord during and shortly after delivery. These stem cells are in the blood at the time of delivery, because they move from the liver, where blood-formation takes place during fetal life, to the bone marrow, where blood is made after birth. Umbilical cord stem cells are similar to stem cells that reside in bone marrow, and can be used for the treatment of leukemia, and other diseases of the blood. Efforts are now being undertaken to collect these cells and store them in freezers for later use. However, one problem is that there may not be enough umbilical cord stem cells in any one sample to transplant into an adult.

Unipotent stem cells
Stem cells that self-renew as well as give rise to a single mature cell type; e.g., spermatogenic stem cells.

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Zygote
The cell that results from the union of sperm and egg during fertilization. Cell division begins after the zygote forms.

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